BULLETIN

de la

Société des Sciences Médicales du Grand-Duché de Luxembourg

N° 1

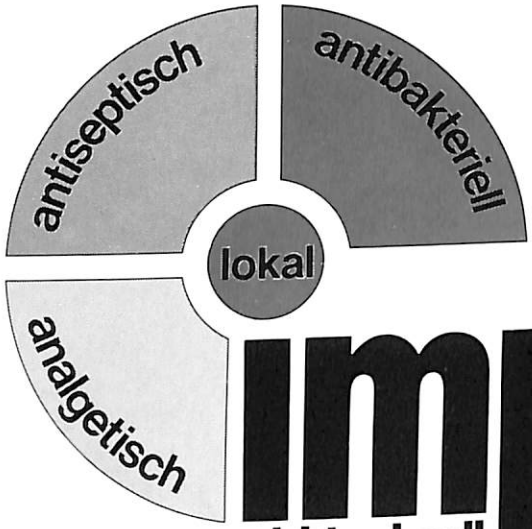
1989 – mars/avril

Die Halstablette mit der Dreifach-Kraft.

1. Das in Imposit enthaltene Gramicidin ist hochwirksam gegen grampositive Erreger wie Staphylokokken, Streptokokken, Pneumokokken, Diphtheriebakterien u.a. Die starke bakterizide Wirkung von Cetylpyridiniumchlorid setzt rasch ein, auch tief in Krypten und Schleimhautfalten.

2. 2,4-Dichlorbenzylalkohol mit seiner ausgeprägten antiseptischen Effektivität gegen grampositive und gramnegative Erreger und Pilze zeichnet sich darüber hinaus durch sehr geringe Toxizität sowie das Fehlen von Resistenzbildung aus.

3. Das Lokalanästhetikum p-Aminobenzoesäureäthylester führt zu rascher Schmerzlinderung und ist besonders geeignet zur oberflächlichen Anwendung auf Schleimhäuten.



imposit®

wirkt schnell, dreifach, antibakteriell.

Imposit®
Zusammensetzung: 1 Tabelle enthält: Gramicidin 0,3 mg, Cetylpyridiniumchlorid 2,0 mg, 2,4-Dichlorbenzylalkohol 2,0 mg, p-Aminobensoesäureathylester 2,0 mg
Indikationen: Bei infektiös-entzündlichen Erkrankungen des Mund-, Hals- und Rachenraumes, Stomatitis, Soor, Gingivitis, Angina tonsillaris und Pharyngitis. Zur Nachbehandlung operativer Eingriffe im Mund-, Rachen- und Kehlkopfbereich sowie bei bakteriellen Sekundärinfektionen im Verlauf einer Virusgrippe.
Nebenwirkungen, Begleiterscheinungen: Bei magenempfindlichen Patienten können nach mehrtätigiger Einnahme gelegentlich Beschwerden wie z.B. Übelkeit auftreten, die meist nach Dosisreduzierung verschwinden.

Dosierung: Tagsüber alle 2 Stunden 1 Tablette im Mund langsam zergehen lassen. Bei Kindern genügt die Einnahme von täglich 4 Tabletten. Tabletten nicht kauen, nicht schlucken. **Hinweis:** Für Diabetiker: 6 Tabletten = ca. 3 g Sorbit = ca. 0,25 BE. **Handelsformen:** O.P. mit 20 Tabletten. **Hersteller:** Dr. Madaus & Co., Köln. **Vertretung: Integral S.A., 5, rue Chr. Plantin, Luxemburg.**

BULLETIN

de la

Société des Sciences Médicales

du Grand-Duché de Luxembourg

Fondé en 1864

N° 1

1989 – mars/avril

Bulletin de la Société des Sciences Médicales du Grand-Duché de Luxembourg

Publié sous la direction du Conseil d'Administration
de la Société des Sciences Médicales, Section des Sciences Médicales
de l'Institut Grand-Ducal

Le Bulletin de la Société des Sciences Médicales du Grand-Duché de Luxembourg publie des articles en français, en allemand et en anglais. Les auteurs sont priés de remettre leurs manuscrits, dactylographiés en double ou triple interligne et en deux exemplaires, au rédacteur en chef.

Les références, classées par ordre alphabétique, doivent comporter dans l'ordre:
a) Le nom des auteurs et les initiales de leurs prénoms, b) le titre du travail, c) le nom du journal, d) le tome, e) la première page de l'article, f) l'année de parution. Pour les citations d'ouvrages, une référence comportera dans l'ordre, outre les noms des auteurs et le titre du livre: a) la ville, b) l'année de parution, c) le nom de la maison d'édition.

Il est recommandé aux auteurs que les articles soient succincts et, si possible, suivis d'un résumé en anglais. Tous les articles seront lus par le rédacteur et un consultant-spécialiste.

Les articles n'engagent que leurs signataires, et sauf avis spécial les opinions exprimées ne reflètent pas nécessairement la position de la Société des Sciences Médicales.

The Bulletin is published two or three times per year and accepts articles in French, German and English. The authors are invited to submit the original copy and a duplicate, typed doublespaced, to the editor. The references, in alphabetical order, should conform to the style of the Index Medicus: Surname and initials of authors, title of article, name of journal, volume number, first page and year.

All the articles, which should be succinct, are reviewed by the editor and a member of the editorial board.

Sommaire

Nomenclature des Laboratoires et Firmes ayant annoncé dans le présent volume

Astra-Nobelpharma
Boehringer Ingelheim
Bournonville & Fils
Comptoir Pharmaceutique Luxembourgeois
Heumann Pharma
Duphar & Cie
Integral S.A., Luxembourg
Intecopharm (Diadal), Madaus, Troponwerke
Janssen Pharmaceutica
Labaz-Sanofi
Marck Sharp & Dohme
Parke Davis
Pharmacia
Pfizer S.A.
Philips S.A., Luxembourg
Prophac S.A., Luxembourg
Boehringer, Fabre, Merrell, Schwarz Pharma
Produits Roche
Salvia Werk GmbH
Schaper & Brümmer
Servier Luxembourg
Upjohn Pharmaceuticals
Will Pharma
Laboratoires Winthrop
Zyma-Galen

Editorial

En cette 125^{e} année de publication du Bulletin de la Société des Sciences Médicales, une tentative est faite, à titre d'innovation et afin d'élargir l'audience, d'une publication conjointe avec «Medical Oncology» de Pergamon Press, Oxford, une des plus grandes maisons d'édition en sciences naturelles.

A l'occasion d'un séminaire qui s'est tenu à Luxembourg en Novembre 1987, des articles nous ont été soumis sur la maladie résiduelle en cancérologie, un des concepts les plus importants actuellement dans ce domaine.

Sur ce, après accord du Conseil d'Administration de la Société des Sciences Médicales et de notre imprimeur, la proposition d'un numéro commun avec Pergamon Press a été retenu et divers autres auteurs ont été contacté afin de pouvoir composer un numéro cohérant sur un seul sujet, à paraître en 1989, «Année de l'Europe contre le cancer».

Le partenaire étant anglosaxon, il a été indispensable de choisir, ce qui est un phénomène en généralisation, l'anglais, langue véhiculaire la plus répandue et commune en sciences naturelles. Il a été dans les traditions du Bulletin d'être trilingue et j'espère que nos lecteurs ne nous tiendront pas rigueur d'un numéro entièrement en anglais.

En espérant que cette expérience soit pleine de succès, je vous en souhaite une lecture instructive et agréable.

M. Dicato
Editeur

Venostasin retard

Traitement de l'insuffisance veineuse

Composition

1 capsule retard contient:
300 mg d'extrait titré, se composant de 240-290 mg d'extrait sec de marron d'Inde et de 60-10 mg de dextrine correspondant à 50 mg de triterpenglucosides calculé en aescine.

Indications

Troubles fonctionnels dans les affections des veines de la jambe (symptômes de l'insuffisance veineuse chronique) – par ex. varices, phlébite, thrombophlébite, s'accompagnant de douleurs dans les jambes, sensation de lourdeur, prurit, crampes nocturnes du mollet, oedèmes, tension et fatigue au niveau des jambes.

Effets indésirables

De légers troubles gastriques peuvent se manifester occasionnellement. Dans ce cas, il est recommandé de prendre le médicament au moment des repas.

Posologie et mode d'emploi

Une capsule retard matin et soir avant les repas (à avaler avec un peu de liquide sans croquer).

Présentation

Boîtes de 50 capsules retard

BOURNONVILLE-PHARMA Parc Industriel de la Vallée du Hain, 1430 B.R. WAUTHIER-BRAINE, tél. 02/384 60 80

The Monitoring of Minimal Residual Disease in Patients with Malignant Tumors

Peter Reizenstein

Division of Hematology, Karolinska Hospital, S-10401 Stockholm, Sweden

INTRODUCTION

The fact that tumor cells frequently remain after treatment is best illustrated by frequent relapses of tumors after treatment with surgery, radiation or cytostatics. One illustration is the recent finding by Rutqvist of an increased incidence of mammary carcinoma as late as 40 years after the treatment of the initial tumor. The present purpose is to discuss some of the possibilities for diagnosis of the presence of minimal volumes of remaining tumor. Oncofoetal tumor markers will, however, be discussed only partially, since there is a separate chapter in this volume dealing with these markers in lung cancer.

It is important to diagnose minimal residual tumors, both to avoid unnecessary treatment and to avoid omission of that which is necessary. (See the section on non-specific methods, below.) Unnecessary adjuvant chemotherapy, for instance, has probably been given both to premenopausal breast cancer patients with negative nodes and to postmenopausal patients (32). Similarly, unnecessary bone marrow transplants may be given to the 15% of young patients with acute myeloid leukemia in complete remission who would be long term survivors even without the marrow transplant. Since the operation mortality is 30–40%, and the average frequency of allogeneic transplants in the Western world is about 3 per million inhabitants per year, around 100 young patients are killed per year in Europe and the U.S.A. by an operation which could have been avoided if minimal residual leukemia could be clinically demonstrated.

Similarly, it is also important to diagnose minimal residual disease to avoid errors of omission. For example, microscopic residual tumors were found at 'second-look' laparotomies in 50 of 246 patients with ovarian cancer. Progressive disease was found in 12 of these patients after 2 years, despite treatment (25), but in 38 there was no progress.

Post-operative residual colon carcinoma would also be important to diagnose, since adjuvant chemo-radiotherapy

could be shown to delay metastasis (37). In 4/13 Burkitts lymphomas with extramedullary involvement, B-cell colonies could be shown to grow in marrow cultures, but not in 54 patients without such involvement (26).

TUMOR-SPECIFIC ANTIGENS

Numerous attempts to identify tumor-specific antigens on human tumor cells have been made. The first, and thus best studied antigen in man, is the so-called common acute lymphatic leukemia antigen (CALLA), originally described by Greaves. It is now well established that this antigen is specific neither for acute lymphatic leukemia, nor for acute leukemia, nor for malignant cells (1,2). It has been found on cells from patients with non-Hodgkin lymphoma (NHL) and chronic lymphatic leukemia (CLL), as well as in tonsillary tissue from patients without any malignant disease (Table 1). In acute lymphatic leukemia in complete remission, CALLA-expressing cells may be seen to appear in the bone marrow and to disappear spontaneously without any signs of relapse (Fig. 1). On the other hand, B-cell cultures from acute lymphatic leukemia blood show more (2–72%) CALLA-positive cells than those from normal blood (3).

It has also been shown that CALLA positive cells from acute lymphatic leukemia patients differ from CALLA positive cells from patients without leukemia in terms of their differentiation capabilities (see chapter by Breard et al., this volume) and it is thus not known whether the cells seen in complete remission in acute leukemia displaying the CALLA antigen are derived from normal or leukemic cells. The possible

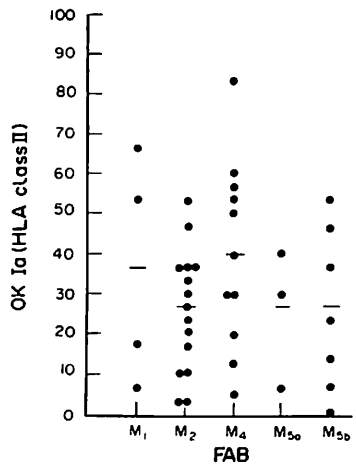


Fig 1. Heterogeneity of HLA-2 expression on cells from patients with acute myeloid leukemia.

normal origin of CALLA-expressing cells explains why patients with over 2% CALLA positive cells during remission have no shorter remission duration than patients with fewer CALLA positive cells.

Leukemic cells of non-lymphatic origin can also display a relatively limited number of CALLA-molecules on their surface (9). It is thus improbable that the CALLA antigen can be used to identify remaining malignant cells. It has not been demonstrated that other tumor-specific or associated antigens can find imperceptible tumors. Oncofoetal antigens, as mentioned above, may constitute an exception regarding recurrences of tumors.

TABLE 1. Per cent cells binding two monoclonal antibodies from the J5 and Vil A1 hybridomas against partially different epitopes on non-malignant lymphatic cells, and cells from patients with non-Hodgkin lymphoma (NHL) chronic (CLL) and acute (ALL) lymphatic leukemia

	%J5 pos. cells	% Vil A1 pos. cells	
Non-malignant tonsils (n = 16)	18.63	9.3	P = 0.0001
NHL and CLL (n = 13)	18.69	6.7	P = 0.05 (P = 0.006)
ALL (n = 19)	13.9	11.4	P > 0.5

TISSUE-ASSOCIATED AND DIFFERENTIATION ANTIGENS

Even if leukemia-specific antigens in man have not been found, it is possible that differentiation or tissue-specific antigens could be of help. However, the antigen expression on tumor cells is very heterogeneous. For instance, HLA-2, which on myeloid cells is a differentiation antigen, can be expressed by anything between all or none of the leukemic cells (Fig. 1, refs. 5,6,7). It is therefore probable that this method offers relatively little hope in the detection of minimal residual tumors when cell-bound antigens are analyzed.

There are, however, some differentiation or carcinoembryonic antigens which are liberated into the serum. The advent of monoclonal antibody RIA tests has made the assays relatively sensitive. Of CA 19-9, a carbohydrate antigen, about 1.4 units (1.1 mg) per ml can be assayed with a coefficient of variation of 10% (8,9,10,11). The sensitivity in gastrointestinal and pancreatic carcinomas varies between 8% in localized colorectal adenocarcinoma to 46% in advanced colorectal or gastric cancer and up to 79–91% in pancreatic cancer (13). It has not been shown that any serum CA 19–9 increase can be found in asymptomatic, small tumors (11,13,14).

Only 0.4% of healthy blood donors have values over 37 units/ml, which has led to claims of specificity of 99.1–99.9% (12). However, in benign liver disease or among smokers, there are between 14 and 58% 'false' positives.

The concentration of the carcinoembryonic antigen, CEA, is higher than the 95% confidence limit in only 23–68% of pancreatic carcinoma patients, (11,13), in 38% of patients with ovarian (15,16) and 39% of gastrointestinal cancer, but also in 17% of patients with benign gastrointestinal disease (13).

Alpha-foetoprotein, a marker for liver carcinoma (16 of 18 cases), is normal in pancreatic cancer and in most patients with biliary 34 tract cancer (13).

A monoclonal antibody (OC125) against a high molecular weight glycoprotein antigen (CA125), is over 35 U/ml in only 1% of healthy and 6% of patients with non-malignant disease, in 29% of patients with gastrointestinal and

TABLE 2. Aneuploidy in patients with acute myeloid leukemia at diagnosis. Flow fluometry, acridine orange, 11 patients with AML

	Mean*	c.v.
Mouse thymocytes	25.9	7.8
Normal human WBC	62.8	7.2
Ac. myel. leukemia cells	74.9	14.1

Correlation coefficient between aneuploidy excess and in vitro growth (CFUC): +0.948, $P < 0.05$.

*Arbitrary fluorescence units.

TABLE 4. Tumor markers (for abbreviations see text), numbers positive in remission, patients with various tumors

	Cut-off value	No.
TPA	130 U/ml	8/38 10/111
CA19-9	37 U/ml	0/22
CA125	65 U/ml	5/22
CEA	2.5 ng/ml	7/22
CRP	20 U/ml	6/38

TABLE 3. Aneuploidy in the bone marrow of patients with acute leukemia (16a) at diagnosis and in remission

	Myeloid	Lymphatic
At diagnosis	In remission	In remission
27% of patients	0	< 10% of patients

breast cancer but in 82% of patients with ovarian carcinoma (48). It is produced and released by ovarian carcinoma cells. Increased values are generally absent in mucinous tumors of the ovary.

Tissue polypeptide antigen (TPA), possibly a cytokeratin-like peptide, is described as less specific in ovarian carcinoma than CA125 (45). CA125 is low (under 25 U/ml) in all remission patients, however, (46) whereas TPA is at least sometimes (10/111 patients) positive (over 130 U/l., refs. 45,47), despite the fact that TPA has been claimed to be present in cells mainly during the S and mitosis phases. *

Most papers dealing with embryonic antigens strive to demonstrate disease progression. Here, the purpose is to discuss minimal residual tumors, i.e. those remaining after, e.g. an operation of ovarian carcinoma. Table 4 suggests that, in this particular respect TPA, CA125 and CEA are more sensitive than CA19-9. However, definitions of remission vary and no proper follow-up has been made of the patients who did have and those who did not have elevated values in one of these results.

TUMOR MARKERS OTHER THAN ANTIGENS: TERMINAL TRANSFERASE, ONCOGEN EXPRESSION, ANEUPLOIDY, MALIGNANT CLONOGENIC CELLS

Tumor markers other than antigens could also be useful in the diagnosis of minimal residual disease. Terminal deoxynucleotidyl transferase (TdT) has been studied in acute lymphatic leukemia by Buchanan (17). He found less than 2% TdT positive cells in normal bone marrow and between 2 and 4% in the marrow from leukemia patients in complete remission. In the peripheral blood, he found 0.04% in healthy subjects. All three patients with over 0.11% TdT-bearing cells in the blood relapsed, but none of the eight patients with less than 0.11%. Hetherington (18) could predict 4/6 marrow relapses by demonstrating TdT-positive cells (0.12-0.22% in blood).

Van Dongen (19) tried to improve the sensitivity of the TdT method to diagnose minimal residual disease by combining it with a monoclonal antibody called WT1. Phenotypes containing terminal transferase alone were found in 0.5-10% of complete remission marrows from patients with acute lymphatic leukemia, but in only 0.01-0.12% of cells in combination with WT1 antigens (9). This method thus holds some promise for future diagnoses of minimal residual disease in acute lymphatic leukemia.

Another interesting approach has also been tried by van Dongen, who looked for activated oncogens in the bone marrow from patients with acute myeloid (AML) and lymphatic (ALL) leukemia in complete remission. He found c-*fes* transcribed RNA in 7% of AML-cells but in no ALL-cells (19). Similarly, EBV-DNA has been demonstrated with cloned probes (20).

The aneuploidy of malignant, particularly highly malignant cells has also been studied. In acute manifest myeloid leukemia bone marrow, a higher coefficient of variation of the cellular DNA content has been found (Table 2), but in complete remission, Barlogie (21) did not find any bone marrow cell aneuploidy. It is, however, possible for flow cytometry to detect as little as 0.02% of aneuploid cells in blood and 0.005% in effusions (22).

Sometimes malignant clonogenic cells can be cultured or found. There are over 20 T-cell cultures per 100 000 blood mononuclear cells in patients with T-cell lymphomas that will relapse, but fewer in those not relapsing and none in B-cell lymphomas (4). A lack of Y-chromosomes is found in some myeloid leukemia cells, but in complete remission there may still be 6-39% Y-negative metaphases.

SENSITIVITY OF THE SAMPLING TECHNIQUE

At the time of diagnosis, the estimated leukemic cell number is 1000 billion, at the time of complete remission, it is assumed to be 1-10 billion.

Even if we assume that we have a perfect marker, absent on all non-neoplastic cells and present on all neoplastic ones, the sensitivity of a marrow sample in detection of residual tumor

* By Dr Fischer, Sales and Marketing Manager, AB Sangtec Medical (1985).

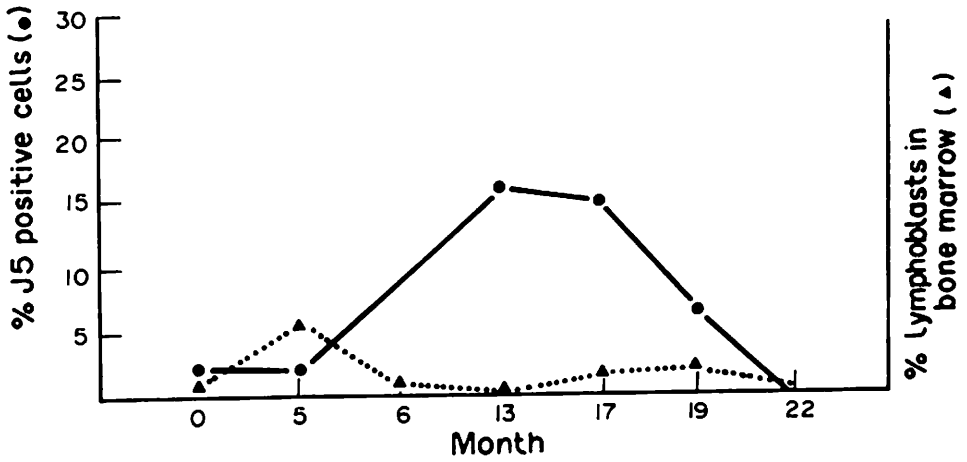


Fig. 2. Percentage of CALLA-positive (O) cells and of lymphoblasts (X) in the bone marrow of a girl in complete remission 5 years after the treatment of acute lymphatic leukemia. Despite abstention from treatment, there was spontaneous regression and no relapse.

would be very limited. There is a relatively limited number (according to van Bekkum 50 million) of bone marrow cells in an ordinary bone marrow biopsy or aspiration. Since one leukemic cell in a sample of 50 million corresponds to 20 000 leukemic cells in the entire 1000 billion marrow cells, this is the sensitivity limit or the number of malignant cells which, even with a perfect marker, would escape detection (24).

The detection limit using the fluorescence-activated cell sorter (FACS) has been reported to be about 2%, and that using a fluorescence microscope to be 0.01% (19). Modern cell sorters seem to have lower threshold and a better sensitivity, however.

NON-SPECIFIC METHODS

Methods based on markers bound to tumor cells, or on ploidy, or on oncogen transcription or amplification can be used only when the site of possible metastases is known, so that tissue samples from this site can be obtained and studied. This, unfortunately, is rarely the case in solid tumors, and therefore the present discussion of the non-specific response, which can be seen even if the tumor site is unknown, may be important.

THE NON-SPECIFIC BIOLOGICAL RESPONSE TO TUMORS

Signs and symptoms of the biological response can perhaps become useful if alternative causes for increases in acute phase reactants, or disturbances of nutritional or conventional immunity are excluded (23).

ACUTE PHASE REACTANTS

The erythrocyte sedimentation rate has been shown by Haybittle to be a statistically significant prognostic predictor in Hodgkin's disease in stages Ia to IIa, in contrast to the much more traumatic restaging laparotomy (27). The ESR is not a good prognostic indicator, on the other hand, in non-Hodgkin lymphoma (30).

The erythrocyte sedimentation rate 1 month after achieving complete remission in acute myeloid leukemia is also a significant predictor. Eleven of 17 patients with less than 40 mm per hour had a remission lasting over 8 months, in contrast to none of the 54 patients with a higher sedimentation rate (41).

Similarly, patients with cervical carcinoma which were found 5 years later to have relapsed had, 1 year after radiotherapy, a mean erythrocyte sedimentation rate of 31 mm

cause a relapse is that between 1 cell and 1 million cells (between 1 pg and 1 mg of tumor tissue) would suffice. These figures are too low, since pretransplant cytoreduction probably does not eliminate all tumor cells, but is assisted by the graft versus leukemia effect, and since the doubling time may become longer as the tumor mass increases. Nevertheless, possibilities for detection of such amounts by direct and specific methods, for instance with the help of tumor specific monoclonal antibodies or with DNA probes, are here suggested to be less promising than those using indirect and nonspecific methods reflecting the biological response to tumors.

REFERENCES

1. CANON C., EICHLER-REISS E., KNAPP W., REIZENSTEIN P. and MATHÉ G.: Difference between monoclonal antibodies against the common acute leukemia antigen from two different hybridomas. Anticancer Res. 3, 407-408, 1983.
2. CANON C., EICHLER-REISS F., REIZENSTEIN P. and MATHÉ G.: Influence of pre-incubation with one antibody on the binding of a second human lymphocytes. Med. Oncol. Tumor Pharmacother. 2, 287-290, 1985.
3. CONSOLINI R., SIMI P., FAVRE A., BOURINBARI A. and BOTTONE E.: CALLA in ALL in complete remission. Leuk. Res. 10, 101, 1986.
4. ALLONCHE M., GEORGOULIAS V., DUPUY C., CLEMENCEAN C. and JASMIN C.: T-colony formation in T-cell malignancy. Leuk. Res. 10, 102, 1986.
5. ÖST A., CHRISTENSSON B., ANDERSSON R., HAST R., LAGERLÖF B., REIZENSTEIN P., TROWBRIDGE S. and BIBERFELD P.: Immune phenotype heterogeneity in AML. Scand. J. Haemat. 34, 293-302, 1985.
6. MIALE T., STENKE L., LINDBLOM J. B., SJÖGREN A. M., REIZENSTEIN P., UDÉN A. M. and LAWSON D. L.: Surface Ia-antigen expression and MLR-stimulating capacity of human leukemic myeloblasts: implications for immunotherapy and prognosis. Acta Haemat. 68, 3-13, 1982.
7. TUBIANA N., LECAER F., LEJEUNE C., HORCHOWSKI N., SEBAHOUN G., PERRIMOND and CARCASSONNE Y.: Immunological detection of residual acute lymphoblastic leukemia. Leuk. Res. 10, 101, 1986.
8. DEL VILLANO B., BRENNAN S., BROCK P., BUCHER C., LIU V., MCCLURE M., RAKE B., SPACE S., WESTRICK B., SCHOEMAKER H. and ZURAWSKI V.: Radioimmunometric assay for a monoclonal antibody-defined tumor marker CA 19-9. Clin. Chem. 29, 549-552, 1983.
9. DEL VILLANO B. and ZURAWSKI V.: The carbohydrate antigenic determinant 19-9 (CA 19-9): a monoclonal antibody defined tumor marker. Immunodiagnostics, 269-282, 1983.
10. KLAPDOR R., LEMANN U., BAHLO M., ACKERN H., DALLECK U. and SCHREIBER W.H.: Ca 19-9 in der diagnostik und differentialdiagnistik des exkretorishen pankreaskarzinoms. Tum. Diag. *Ther.* 5, 1983.
11. VAN BECKUM D. W.: Residual reflections on the detection and treatment of leukemia, in LÖWENBERG B. and HAGENBEEK A. (eds): Minimal Residual Disease in Acute Leukemia, pp. 385-396. Boston, Martinus Nijhoff, 1984.
12. RITTS R., DEL VILLANO B., GO V. L. W., HEBBERMAN R., KLUG T. and ZURAWSKI V.: Initial clinical evaluation of an immunoradiometric assay for CA 19-9 using the NCI serum bank, Int. J. Cancer 33, 339-345, 1984.
13. JALANKO H., KUUSELA P., ROBERTS P., SIPPONEN P., HAGLUND C. and MÄKELÄ O.: Comparison of a new tumour marker, CA 19-9 tm, with alfa-fetoprotein and carcinoembryonic antigen in patients with upper gastrointestinal diseases, J. clin. Path. 37, 218-222, 1984.
14. WIECHEL K.-L., WAHREN B and HARMENBERG U.: Markers for tumors in pancreas cancer are too uncertain to be used

„Dickes Bein“ • Postthrombophlebitisches Syndrom • Ulcus cruris

Venalot®

trifft Stauung · Entzündung · Ödem · Schmerz

beseitigt Schweregefühl und Schmerzen

bessert venöse Zirkulationsstörungen

befreit das Interstitium von angehäuften Plasma-Proteinen

mobilisiert den Lymphstrom

Zusammensetzung: 1 Kapsel enthält: Extr. Melilot. stand. sicc. 25 mg. (Cumaringehalt 5 mg). Rutosid 25 mg. **1 Ampulle** zu 2 ml/5 ml enthält Extr. Herb. Melilot stand. 10 mg/25 mg (Cumaringehalt 3 mg/7,5 mg). Rutosidschwefelsäureester, Natriumsalze 50 mg/125 mg. **1 Depotdragée** enthält: Cumarin 15 mg, Troxerutin 90 mg. **10 ml Liniment** enthalten: Extr. Herb. Melilot. stand. 5 ml (Cumaringehalt 50 mg), Heparin 500 I. E. **Kontraindikationen:** sind bisher nicht bekannt. **Nebenwirkungen:** wurden bisher nicht beobachtet.
Depot: mathis prost s.a. 4, rue du fort wallis, 1019 Luxembourg.

Dosierung: Oral: Venalot®-Depot: 3 x täglich 1 – 2 Dragées. **Venalot®-Kapseln:** 3 x täglich 1 – 2 Kapseln.
Parenteral: 2 – 5 ml i.v. oder i.m. **Venalot®-Liniment:** mehrmals täglich die erkrankten Stellen einreiben.
Darreichungsformen und Packungsgrößen: Kapseln 50 St., 100 St., AP 500 St.; Ampullen 5 x 2 ml. AP 100 x 2 ml; 5 x 5 ml, 10 x 5 ml. AP 100 x 5 ml; Liniment 70 ml, 150 ml, AP 700 ml; Depot-Dragées 20 St., 50 St., 100 St., AP 1000 St.; (Stand: September 1988).

Schaper & Brümmer
D 3320 Salzgitter - Ringelheim
Naturstoff-Forschung und -Therapie

HYPERLIPIDEMIES

HYPERLIPEN

CIPROFIBRATE

efficace avec

1

prise / jour

Laboratoires WINTHROP s.a. - Rue Franz Merjay 103 - 1060 BRUXELLES

in risk-groups, Läkartidningen, V 82, 1985.

15. BAST R., KLUG T., JOHN E., JENISON E., NILOFF J., LAZARUS H., BERKOWITZ R., LEAVITT T., GRIFFITHS T., PARKER L., ZURAWSKI. V. and KNAPP R.: A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. New Engl. J. Med. 309-15, 883-887, 1983.
16. BAST R., KLUG T., SCADTZL E., LAVIN P., NILOFF J., GREBER T., ZURAWSKI V. and KNAPP R.: Monitoring human ovarian carcinoma with a combination of CA 125, CA 19-9, and carcinoembryonic antigen. Am. J. Obstet. Gynec. 149-5, 553-559, 1984.
17. BUCHANAN G. R. and SMITH R. G.: Detection of early relapse and minimal residual disease in children with acute lymphoblastic leukemia by enumeration of terminal deoxynucleotidyl transferase-positive cells in peripheral blood, in LÖWENBERG B. and HAGENBEEK A. (eds): Minimal Residual Disease in Acute Leukemia, pp. 83-95. Boston, MA, Martinus Nijhoff, 1984.
18. HETHERINGTON M., HUNTSMAN P., SMITH R. and BUCHANAN, G.: Surveillance of TdT containing cells in ALL. Leuk. Res. 10, 100, 1986.
19. VAN DONGEN J. J. M., HOOIJKAAS H., KAHLEN K., BENNE K., BITTER W. M., VAN DER LINDE-PREESMAN A. A., TETTERO I. L. M., VAN DE RIJN M., HILGERS G. E., VAN ZANEN G. E. and HAGEMEIJER A.: Detection of minimal residual disease in TdT positive T cell malignancies by double immunofluorescence staining, in LÖWENBERG B. and HAGENBEEK A. (eds): Minimal Residual Disease in Acute Leukemia, pp. 67-81. Boston, MA, Martinus Nijhoff, 1984.
20. ANDIMAN W., GRADOVILLE L., HESTON L., NEYDORFF R., SAVAGE M. E., KITCHINGMAN G., SHEDD D. and MILLER G.: Use of cloned probes to detect Epstein-Barr viral DNA in tissues of patients with neoplastic and lymphoproliferative diseases. J. infect. Dis. 148, 967-977, 1983.
21. BARLOGIE B., HITTELMAN W. N., DAVIS F. M. and KANTARJIAN H.: Nucleic cytometry, interphase chromosomes and nucleolar antigen in the detection of residual leukemia in morphologic remission, in LÖWENBERG B. and HAGENBEEK A. (eds): Minimal Residual Disease in Acute Leukemia, pp. 1-18. Boston, MA, Martinus Nijhoff, 1984.
22. WALLE A. and NIEDERMAYER W.: Screening patients for minimal disease. Leuk. Res. 10, 105, 1986.
23. TILLY H., BASTARD C., CASTAIGNE S., BIZET M., PIGNET H. and DEGOS L.: Persistence of Y-cells in a case of acute myeloid leukemia in remission. Leuk. Res. 10, 106, 1986.
24. VAN BECKUM N.: Concluding remarks, in LÖWENBERG B. and HAGENBEEK A. (eds): Minimal Residual Disease in Acute Leukemia. Boston, MA, Martinus Nijhoff, 1984.
25. COPELAND L., GERSHENSON D., WHARTON T., ATKINSON N., SNEIGE N., EDWARDS C. and RUTLEDGE F.: Microscopic disease at second-look laparotomy on advanced ovarian cancer. Cancer 55, 472-478, 1985.
26. PINKERTON C., PHILIP I., FAVROT M. and PHILIP T.: Liquid cultures for the detection of marrow involvement in Burkitts disease. Leuk. Res. 10, 104, 1986.
27. HAUBITTLE N., in LÖWENBERG B. and HAGENBEEK A.: Minimal Residual Disease in Acute Leukemia. Boston, MA, Martinus Nijhoff, 1984.
28. BRIZZI A., OGIER C. and REIZENSTEIN P.: Remission with high erythrocyte sedimentation rates in acute myeloid leukemia is of short duration. Blut 51, 299-300, 1985.
29. EINHORN N. and REIZENSTEIN P.: Secondary anaemia in malignancy. Prognostic significance of haemat. changes six years after irradiation of cervical carcinoma. Acta Rad. 13, 281-287, 1984.

30. HAGBERG H., GLIMELIUS B., GRONWITZ S., KILLANDER A., KALLANDER C. and SCHRODER T.: Biochemical markers in non-Hodgkin's lymphoma stages III and IV and prognosis: a multivariate analysis. Scand. J. Haemat. 33, 59-67, 1984.

31. DI MARTINO G., IANNUCCI F. and IACONO G.: CEA, ferritin, and calcitonin in colorectal and lung cancer—correlation with other types of neoplasms and non-neoplastic diseases. Tum. Diag. Ther. 3, 74-78, 1982.

32. MALLYA R. K., HIND C. R. K. , BERRY H. and PEPUS M. B.: Serum C-reactive protein in polymyalgia rheumatica. S prospective serial study. Arthritis Rheum. 28, 383-387, 1985.

33. HARLEY J. B., ROSARI M. O., YAMAGATA H., FOX O. F. and KOREN E.: Immunologic and structural studies of the lupus/Sjögren's syndrome autoantigen, La/SBB, with a monoclonal antibody. J. clin. Invest. 76, 801-806, 1985.

34. VAN DALEN A., FAVIER J. and EASTHAM W.: Initial experience with TPA, CA125 and CRP as tumor markers in ovarian malignancy.

35. RICERCA B. M., IMPROTA T., D'ONOFRIO G., RUMI C., MANCINI R., MIGGIANO G., STORTI S., MANGO G. and BIZZI B.: Serum lactate dehydrogehase isoenzyme pattern in acute transformation of chronic granulocytic leukemia. Haematologica 71, 20-24, 1986.

36. ELLIOT M. S., LEVENSTEIN J. H., WRIGHT J. P.: Faecal occult blood testing in the detection of colorectal cancer. Br. J. Surg. 71, 785-786, 1984.

37. Prolongation of the disease-free interval in surgically treated rectal carcinoma. Engl. J. Med. 312/23, 1465-1472, 1985.

38. REIZENSTEIN P.: Biologic Response to Disease—the Haematological Stress Syndrome. New York, Praeger, 1983.

39. GOBBI P., GENDARINI A., CREMA A., CAVALLI C., ATTARDO-PARRINELLO G., FEDERICO M., DI PRISCO U. and ASCARI, E.: Serum albumin in Hodgkin's disease. Cancer 55, 389-393, 1985.

40. REIZENSTEIN P., OGIER C. and SJÖGREN A.-M.: Immunotherapy versus chemotherapy of acute myeloid leukemia: response to PHA, allogeneic lymphocytes, and leukemic myeloblasts of remission lymphocytes from leukemia patients. Rec. Results Cancer Res. 75, 29-36, 1980.

41. BRIZZI A., OGIER C. and REIZENSTEIN P.: Remission with high erythrocyte sedimentation rates in acute myeloid leukemia is of short duration. Blut 51, 299-300, 1985.

42 BERAN M., REIZENSTEIN P. and UDÉN, A.-M.: Response to treatment in acute non-lymphatic leukemia: prognostic value of colony forming and colony stimulating capacities of bone marrow and blood cells compared to other parameters. Br. J. Haemat. 44, 39-50, 1980.

43. REIZENSTEIN P., ANDERSSON B. and BERAN M.: Possible mechanisms of immunotherapy action in acute nonlymphatic leukemia: macrophage production of colonystimulating activity. Rec. Results Cancer Res. 80, 64-69, 1982.

44. FREI J.: Acute leukemia in children. Cancer 53, 2019, 1984.

45. KABAWAT S., BAST R., WELCH W. and KNAPP R.: Immunopathologic characterization of a monoclonal antibody that recognizes common surface antigens of human ovarian tumors of serous, endometrioid, and clear cell types. Am. clin. Path. 79 (1), 1983.

46. VAN DALEN A., FAVIER J. and EASTHAM W.: Preliminary observations with new monoclonal antibody in ovarian carcinoma. Tum. Diag. Ther. 5, 67-69, 1984.

47. VAN DALEN A., FAVIER J. and EASTHAM W.: Serum levels of TPA and CA 12-5 in patients with ovarian carcinoma.

48. KLUG T., BAST R., NILOFF J., KNAPP R. and ZURAWSKI V.: Monoclonal antibody immunoradiometric assay for an antigenic determinant (CA 125) associated with human epithelial ovarian carcinomas. Cancer Res. 44, 1048-1053, 1984.

Serum Lipid-bound Sialic Acid as a Tumoral Marker in Minimal Residual Tumors

M. Musset, G. Mathé and P. Reizenstein

Abstract

The lipid-associated sialic acid (LASA) level in serum was increased in 663 out of 794 patients (83.5%) of which 55.1% were CEA negative. Therè were 16.5% LASA (possibly false) negative, CEA positive patients. There were 24.1% false positives in 116 patients without malignant tumors. In manifest prostatic carcinoma 94.2% of the LASA values but only 36.5% of the prostatic acid phosphatase values were increased. Similarly, in breast and pulmonary carcinoma, LASA was more sensitive than CEA. In 499 patients with minimal residual disease, 203 (41.5%) were LASA-negative, of which 180 were CEA-negative.

Out of 180 LASA positive patients, 70 have relapsed, as have 70 out of 219 patients with increases in both LASA and CEA.

The sensitivity of LASA (87%) in lymphoma was higher than that of the erythrocyte sedimentation rate (53.3%), of C-reactive protein (51.2%), serum copper (64.7%) and of six other markers.

INTRODUCTION

The use of biological markers in lung cancer and gynecological tumors has been described in this volume by Karrer. The carcinoembryonic antigen (CEA) is relatively insensitive, positive only in 49–78% of patients with gastro-intestinal cancer. Although it is not specific for malignant tumors, it is frequently used for post-operative monitoring.

Lipid-associated sialic acid (LASA), first described by Katopodis and Stock, is found in high concentration in malignant cells and their membranes. Recent methods used in determining serum concentrations of LASA have shown increased levels. Since claims have been made for in some tumors of a sensitivity approaching 99% and as specificity approaching 94%, the present study was performed in an attempt to study the sensitivity and the specificity of this test.

Service des Maladies Sanguines et Tumorales & ICIG (Université Paris-Sud, CNRS UA 04-1163), Hôpital Paul-Brousse, 94800-Villejuif, France

Division of Hematology, Karolinska Hospital, S-10401 Stockholm, Sweden

This study compares the serum LASA values to the CEA for carcinomas of the breast, lung, head and neck, as well as for soft tissue sarcomas and melanoma. The results in prostatic carcinoma were compared to CEA and to the serum level of the prostatic acid phosphatases (PAP). In malignant lymphomas, the serum LASA levels were compared to β-2 microglobulin, the erythrocyte sedimentation rate, ferritin, serum copper, fibrinogen, LDH, coeruloplasmin, alkaline phosphatase and C-reactive protein (1,2).

The biochemical alterations of plasma membrane gangliosides (sialo-glyco-sphingo-lipids) in tumors have been well documented. Striking modifications of the molecular composition of these acidic glycolipids occur during transformation of mammalian cells in culture by oncogenic DNA viruses (3), by chemical carcinogens or by radiation (4). It has also been shown that gangliosides are involved in cellular interactions (5) and in tumorigenesis (6–8). Along with other glycolipids and glycoproteins, they have been implicated as specific membrane receptors (9). It has also been suggested that cell surface sialic acid may be correlated with tumor metastasis (10).

Special attention has been focussed on the changes of ganglioside composition and the level of their common building block, *N*-acetyl neuraminic acid (sialic acid) in transformed cells. Thus, gangliosides, shed along with other membrane components, emerge as potential tumor markers. The levels of ganglioside-bound sialic acid have been studied extensively in tumor-bearing animals (11–15) as well as in humans (16,17).

Gangliosides and cancer

High density lipoproteins (HDL) are increased in tumor patients and normalised after surgical treatment. Relatively intensive attempts at characterisation have resulted in the identification, first of a proteo-lipid, later called a neo-proteo-lipid, and finally of sialogangliosides also found in cell membranes. For this reason, attempts to estimate sialic acid in the serum of patients with malignant disease were performed. They were successful, and a correlation was finally established between the serum concentration of LASA and the tumor mass.

MATERIALS AND METHODS

The malignant cell membranes contain mono- and disialogangliosides, which may sometimes include abnormal gangliosides or non-ganglioside glycolipids.

The LASA determination

Initial determination methods, including extraction, dialysis, thin layer chromatography and regular chromatography, were too laborious for clinical use. These early methods were simplified by measuring the total gangliosides. In this way the volume of the serum sample could be reduced and a rapid test was developed. A number of studies have confirmed the value of this rapid test as a biological marker of malignancy.

LASA was determined in EDTA vacutainer tubes after centrifugation, dilution at 0°C, methanol and chloroform extraction, centrifugation, phosphotungstic acid precipitation, centrifugation, colouring with resorcinol and spectophotometry at 580nm (18).

The LASA was expressed in mg/dl and values of more than 17.1 ml/dl were considered above the upper limit of the normal range.

PATIENTS

The study included 1547 patients, of which 1283 had solid tumors, 148 malignant lymphomas and 116 control patients without malignant tumors.

The histologic type, anatomical origin, subgroups of the tumors and the clinical condition of the patients has been described elsewhere (1,2).

RESULTS

Of the 1283 patients having solid tumors, 794 were studied in the clinically perceptible phase of their disease and 489 were studied in the stage of minimal residual disease.

Of the 794 clinically perceptible solid tumors, 663 (or 83.5%) were LASA positive, of which no less than 438 (or 55.1%) were CEA negative. On the other hand, of 131 (or 16.5%) LASA negative patients 62 (or 87.3%) were CEA positive. Although the CEA in these latter cases could have been caused by inflammatory or other factors apart from the tumor itself, it seems prudent to regard the 62 cases as false-negative.

It has to be emphasized that while the sensitivity of the LASA test in the entire case-mix of clinically perceptible solid tumors was 83.5%, it achieved 94.2% in prostatic carcinoma and 89% in patients bearing squamous cell carcinomas of different origin such as lung, cervix, vagina, skin, oesophagus or larynx.

In prostatic carcinoma the serum levels of LASA, CEA and PAP (prostatic acid phosphatase) were studied. Fifty-two studies were performed using 23 patients; 25% of the CEA-tests, 36.5% of PAP and 94.2% of LASA were positive. The LASA serum level seems to be a good tool for monitoring the treatment of these patients.

In 306 patients with breast carcinoma, 84.8% of the LASA tests were positive as compared to 44.7% for CEA. When both tests were considered simultaneously, 88.8% of the patients had one of the two positive. Of the primary tumors, prior to operation 65.3% were LASA positive, as compared to 16.4% CEA positive.

In patients with pulmonary metastases, in contrast, 85.7% were LASA positive and only 14.3% CEA positive, and in patients with cutaneous or lymph node metastases, 87% were LASA positive as compared to only 12.5% CEA positive. This suggests that LASA is a more sensitive tumor marker than CEA.

Minimal residual tumors

Of 489 minimal residual imperceptible tumors, 286 (or 58.5%) were LASA negative, of which 270 were at the same time CEA negative and 16 CEA positive.

Altogether 203 (or 41.5%) of these tumors were LASA positive, of which 180 were CEA negative and 23 CEA positive.

Among the 23 cases having both the CEA and LASA positive, 14 have already relapsed or metastasized and among the 16 LASA negative but CEA positive cases, 5 have also relapsed or metastasized.

Among the 180 LASA positive but CEA negative cases, 51 (or 28.3%) have relapsed or metastasized. Most of these patients have breast cancer.

This suggests that among the 219 patients having only one of the two markers at a pathological level (203 LASA + CEA and 16 CEA + LASA) 70 presented early relapses or metastases.

Malignant lymphoma

The study included 148 patients with malignant lymphoma. For both Hodgkin and non-Hodgkin lymphomas, the serum LASA was found at pathologic levels in 87% of cases in the perceptible phase of the disease.

The value of LASA as a biological tumor marker was compared to that of 10 others: ß-2 microglobulin, erythrocyte sedimentation rate, fibrinogen, ferritin, haptoglobin, C-reactive protein, serum copper, alkaline phosphatases, coeruloplasmin and LDH.

For LASA, 87% of samples were positive, as compared to 53.3% of sedimentation rates, 51.2% of C-reactive proteins and 64.7% of the serum coppers. These four were the most sensitive of the ten mentioned above.

Patients without malignant tumors

The study includes 116 patients without malignant disease (control patients). In this group, 88 patients out of 116 (75.9%) had a serum level less than 17.1μg/ml, which is the upper normal limit value. In the 116 patients, we found 28 (24.1%) false positives.

Among 85 patients with apparently benign fibrocystic disease of the breast, 21.2% (18/45 cases) were LASA positive. In two of these patients breast cancer was discovered about 1 year later.

REFERENCES

1. GINSBOURG M., MUSSET M., MISSET J.L. and MATHÉ G.: Relationship between

proliferative activity of bone marrow micrometastasis and plasmatic level of a new cancer marker: lipid associated sialic acid (LASA) in human breast cancer. Biomed. Pharmacother. 40, 388-391, 1986.

2. MUSSET M.: Paper given to International Congress Tumor Markers, Naples, September 1987.
3. BRADY R.O. and FISHMAN P.H.: Membranes of transformed mammalian cells, in FOX C.F. (ed.): Biochemistry of Cell Walls and Membranes, vol. 2, pp. 61-96. MTP Int. Rev. Sci. Biochem. Serie 1, London, University Park Press; Baltimore, Butterworth, 1975.
4. COLEMAN P.L., FISHMAN P.H., BRADY R.O. and TODARO G.J.: Altered ganglioside biosynthesis in mouse cell cultures following transformation with chemical carcinogens and X-irradiation. J. biol. Chem. 250, 55-60, 1975.
5. ROSEMAN S.: Synthesis of complex carbohydrates by multiglycosyl transferase systems and their potential function in intercellular adhesion. Chem. Phys. Lipids 5, 270-297, 1970.
6. BRADY R.O., MORA P.T., KOLODNY E.H. and BOREK C.: Ganglioside metabolism in virally transformed and chemically induced hepatoma cell lines. Fedn. Proc. Fedn Am. Soc. exp. Biol. 29, 410-417, 1970.
7. CUMAR F.A., BRADY R.O., KOLODNY E.H., MCFARLAND V.W. and MORA P.T.: Enzymic block in the synthesis of gangliosides in DNA virus transformed tumorogenic mouse cell lines. Proc. natn. Acad. Sci. U.S.A. 67, 757-764, 1970.
8. HAKOMORI S.I. and MUROKAMI W.T.: Glycolipids of namster fibroblasts and derived malignant-transformed cell lines. Proc. natn. Acad. Sci. U.S.A. 59, 254-261, 1968.
9. CUATRECASES P.: Membrane receptors. Ann. Rev. Biochem. 43, 169-214, 1947.
10. YOGEESWARAM G. and SALK P.L.: Metastatic potential is positively correlated with cell surface syalization of cultured murine tumor cell lines. Science 212, 1514-1516, 1981.
11. KLOPPEL T.M., FRANZ C.P. and MORRÉ D.J.: Serum sialic acid levels increased in tumor bearing dogs. Am. J. Vet. Res. 39, 1377-1380, 1978.
12. KLOPPEL T.M., RICHARDSON R.C., TRAVER D.S. and MORRÉ D.J.: Serum lipid-associated sialic acid values of horses with neoplasm. Am. J. Vet. Res. 42, 1829-1830, 1981.
13. LENGLE E.E.: Increased levels of lipid-bound sialic acid in thymic lymphocytes and plasma from leukemic AkR/J mice. J. natn. Cancer Inst. 62, 1565-1567, 1979.
14. MORRÉ D.J., KLOPPEL T.M., MERRITT W.D. and KEENAN T.W.: Glycolipids as indicators of tumorigenesis. J. Supramol. Struc. 9, 157-177, 1978.
15. SKIPSKI V.P., KATOPODIS N., PRENDERGAST J.S. and STOCK C.C.: Gangliosides in blood serum of normal rats and Morris hepatoma 5123 fc-bearing rats. Biochem. biophys. Res. Commun. 67, 1122-1127, 1975.
16. DMISTRIAN A.M., SCHWARTZ M.K., KATOPODIS N., FRACCHIA A.A. and STOCK C.C.: Serum lipid-bound sialic acid as a marker in breast cancer. Cancer 50, 1815-1819, 1982.
17. PORTOUKALIAN J., ZWINGLESTEIN G., ABDUL-MALAK N. and DORÉ J.F.: Alterations of gangliosides in plasma and red cells of human bearing melanoma tumors. Biochem. biophys. Res. Commun. 85, 916-920, 1978.
18. KATOPODIS N., HIRSHAUT Y., GELLER N.L. and STOCK C.C.: Lipid associated sialic and test for the detection of human cancer. Cancer Res. 52, 5270, 1982.

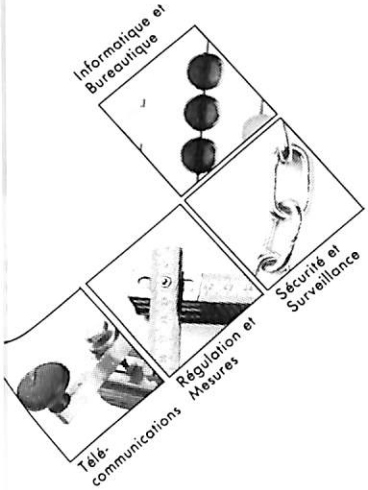
GO PRO

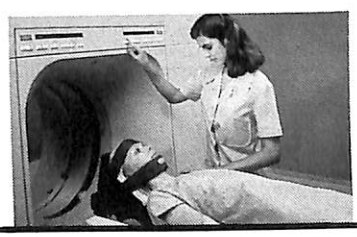
SYSTEMES MEDICAUX

Avant de vouloir aider quelqu'un, il faut être sûr de ne pas lui nuire.

Si, à qualité égale, vous pouvez visualiser l'intérieur du corps humain en limitant l'emploi des rayons X, cela vaut mieux pour la santé du patient.

Tout en améliorant continuellement les appareils à rayons X, Philips pousse le développement d'alternatives. Le diagnostic à ultrasons a été un premier pas, l'imagerie par résonance magnétique le pas suivant dans le développement de techniques de diagnostic encore plus sûres pour le patient.





PROFESSIONAL SYSTEMS
4, rue des Joncs Z.I. Howald - Tél: 49 61 11

PHILIPS

PHILIPS

Alle magen Soluga-stril® Spasmo-

Zusammensetzung: Gel 10 g (1 Beutel) enthalten: Butinolinphosphat 0,002 g, Aluminiumhydroxid-Gel (12,5%, berechnet als Al_2O_3) 3,48 g, Calciumcarbonat 0,6 g. Tabletten: 1 Tablette enthält: Butinolinphosphat 0,002 g, Aluminiumhydroxid-Trockengel (50%, berechnet als Al_2O_3) 0,2 g, Calciumcarbonat 0,3 g. Indikationen: Krampf- und Säureschmerzen bei Gastritis, Duodenitis, Ulcus ventriculi et duodeni, Völlegefühl, Sodbrennen, Magenbeschwerden durch Diätfehler und Medikamente. Kontraindikationen: Engwinkelglaukom, Prostataadenom mit Restharnbildung, mechanische Stenosen im Bereich des Magen-Darm-Kanals, Tachyarrhythmie, Megacolon. Nebenwirkungen: Mundtrockenheit, Abnahme der Schweißdrüsensekretion, Hautrötung, Akkomodationsstörungen, Glaukomauslösung, Tachykardie, Miktionsbeschwerden. Wechselwirkungen: Bei gleichzeitiger Gabe von Amantadin, Chinidin oder trizyklischen Antidepressiva kann die Wirkung von Butinolinphosphat verstärkt sein. Das Präparat kann die Resorption von wichtigen Nahrungsbestandteilen und Arzneimitteln (Eisen-haltige; Tetrazykline; Chenodesoxycholsäure-haltige) beeinträchtigen. Hinweise: Bei schweren Nierenfunktionsstörungen ist eine hochdosierte Daueranwendung, über 6 Beutel bzw. 12 Tabletten pro Tag, zu vermeiden. Dieses Arzneimittel kann auch bei bestimmungsgemäßem Gebrauch das Reaktionsvermögen soweit verändern, daß die Fähigkeit zur aktiven Teilnahme am Straßenverkehr oder zum Bedienen von Maschinen beeinträchtigt wird. Dies gilt in verstärktem Maße im Zusammenwirken mit Alkohol. Dosierung und Art der Anwendung: Bei Säure- und Magenbeschwerden 3mal täglich 1-2 Stunden nach den Mahlzeiten sowie zusätzlich vor dem Schlafengehen und bei zwischenzeitlich auftretenden Magenbeschwerden den Inhalt eines Einzelbeutels einnehmen bzw. 1-2 Tabletten zerkauen und mit oder ohne Flüssigkeit schlucken.

Darreichungsformen und Packungsgrößen: Packung mit 20 Einzelbeuteln Gel, Packung mit 50 Einzelbeuteln Gel, Packung mit 20 Tabletten, Packung mit 50 Tabletten, Packung mit 100 Tabletten.

HEUMANN PHARMA GMBH & CO · D-8500 NÜRNBERG

Littérature et échantillons: Comptoir Pharmaceutique Luxembourgeois S.A., Luxembourg

Stand: Januar 1986

HEUMANN PHARMA

Diagnostic and Prognostic Importance of Tumor Markers in Lung Cancer

E. Ulsperger and K. Karrer

INTRODUCTION

There is an accumulating body of evidence that patients with cancer have an increased incidence of elevated levels of factors in their blood which are associated with tumor disease. We have long sought to define those specific substances which can be used to diagnose or assist in the diagnosis of malignant tumors.

'Tumor markers' refers to substances found in blood or in other bodily fluids (urine, ascites, pleura, cerebrospinal fluid, etc.), as well as on the surface of malignant cells. They can be classified as Table 1 and characterized as in Table 2 (1).

These markers are produced or induced by tumor cells and they are associated with malignant tumors more than any other laboratory measurements.

Many investigations into this subject have made available a great number of tumor-derived products in lung cancer patients, but the ideal tumor marker, defined by the characteristics given in Table 2, has not yet been found.

At present, only surgery is of major prognostic importance in the treatment of non-small cell lung cancer and—according to the Viennese Medical School—also for small cell lung cancer at the early stages (2). Accordingly, the main role of markers in these patients would be to distinguish between operable and inoperable patients and to detect and predict residual disease postoperatively, as well as relapsing tumor or metastases.

Conversely, patients with advanced small cell lung cancer are more often treated primarily with chemotherapy. In these patients it would be of considerable interest to have markers indicating the tumor load and response to treatment.

THE ONCOFOETAL ANTIGEN CEA

Gold and Freedmans' description of the carcinoembryonic antigen (CEA) in 1965, thought to be specific only for colonic cancer, was the beginning of modern tumor marker research (3). The glycoprotein CEA shows a molecular weight of 180 000

Institute for Epidemiology of Neoplasms of the University of Vienna, Borschkegasse 8a, A-1090 Vienna, Austria

TABLE 1. Classification of human tumor markers in lung cancer

Hormones
Adrenocorticotropin (ACTH)
Antidiuretic hormone (ADH)
Calcitonin
β-endorphine
Gastrin
Glucagon
Growth hormone
Insulin
Lactate dehydrogenase
Lipotropophic hormone (LPH)
Melanocyte-stimulating hormone (MSH)
Oxytocin
Parathormone
Prostaglandin
Secrtein
Oncofoetal antigens
Carcinoembryonic antigen (CEA)
Tissue polypeptide antigen (TPA)
Enzymes
Fucosyl transferase
Lactic dehydrogenase
Neuron specific enolase (NSE)
Sialyl transferase
Proteins
α_1-acid glycoprotein
Bombesin
β_2-microglobulin
Ferritin
Pregnancy-associated macroglobulin (PAM)
Immunoglobulines
IgG
IgA
IgM
Others
Zinc

and contains a carbohydrate consisting of *N*-acetyl glucosamin, mannose, galactose, fucose and siliac acid (4).

Following its description by Lo Gerfo, who first detected CEA in the sera of lung cancer patients, CEA is now clinically applied, but its use is equivocal and it has been found that this marker is associated with many different neoplasms as well as non-neoplastic disease (5,6). For example, patients with chronic bronchitis, cor pulmonale, pulmonary tuberculosis and heavy smokers show elevated levels, while, on the other hand, a trial detected normal CEA values (2.5 ng/ml) in about 40% of patients with a lung tumor (7,8).

CEA measurement correlates with the degree of progress and the prognosis, as highly elevated CEA values are associated with

TABLE 2. Characteristics of an ideal tumor marker

1. Produced only by the tumor cell.
2. Detectable in bodily fluids (blood, urine).
3. No level in benign diseases or healthy persons.
4. Detactable levels in early diseases for screening.
5. Correlation between marker level and tumor bulk.
6. A present malignant disease, clinically not evident, is indicated by the marker.
7. Correlation between marker level and effect of antineo-plastic treatment.
8. Identification of tumor cell type.

'bad' prognosis and can be of clinical importance as an additional clinical estimation to determine survival, particularly for patients with extrathoracic disease. It was found by investigators that patients with preoperative CEA levels of 6 ng/ml or less survived longer—more than 3 years—than patients with levels in excess of 6 ng/ml. Also the double CEA determination measuring bronchial and serum CEA levels, offers a discriminative value between the primary or metastatic nature of malignant disease. Laurence even showed that CEA levels related to the stage of the tumor (9–12).

A number of authors have tried to make CEA investigations more attractive by combined determinations. Dent found in his analysis of the correlation of CEA and C1q-binding activity (C1q-BA), that patients with an elevation of CEA and C1q-BA during the immediate postoperative period show significantly shorter survival times. It appears that the CEA estimation has the best predictive value, but the addition of C1q-BA measurements may provide additional prognostic information, particularly in patients who do not have elevated CEA levels (13).

In trying to find a correlation between the histological tumor type and CEA measurements, several investigators have found significantly elevated CEA levels in adenocarcinoma and small cell carcinoma of the lung (14–17).

Severely elevated pretreatment levels indicate an advanced disease, often referring to liver metastases. CEA values, greater than 5 ng/ml, show falling levels at response to chemotherapy, and a rise when resistance to chemotherapy develops. This good correlation of marker value and treatment is not perceptible in patients with pretreatment levels below 5 ng/ml. But the prognosis for these patients is much better. In some cases CEA measurement is able to predict a relapse (3,18,19).

THE ENZYME NSE

Neuron-specific enolase (NSE) is the neuronal form of interzytoplasmatic glycolytic enzyme enolase which was first found in extracts of brain tissue and later in neuroendocrine cells and neuroendocrine tumors including SCCL. In contrast, NSE has not been demonstrated in non-endocrine tumors (20).

It is thought that small cell carcinoma of the lung is of neuroendocrinic origin. NSE is elevated on average in only 14% of patients with non-SCCL (5,6) Conversely, NSE has been found to be elevated in 65% of SCCL patients (Table 3) (21–28).

Serum NSE levels change in parallel with the clinical course during therapy. Using serial NSE determination, Johnson found in 80% (40 out of 50 patients) that NSE levels fell on the patients' response to treatment, and increased in five out of seven with the progression of the disease, and increased in 30 out of 35 (85%) of patients who relapsed. It is suggested that the serum NSE may be a useful marker for monitoring the clinical course in lung tumor patients, especially in SCCL.

Johnson found in 30 out of 35 (85%) patients who relapsed an elevated marker level (>20 ng/ml) and in 15 out of 23 patients a persistent

TABLE 3. Percentage of neuron-specific enolase elevation in SCCL

Limited	%	Extensive	%	Level	Reference
15/38	39	49/65	87	>12 ng/ml	21
23/39	59	45/54	83	>20 ng/ml	22
34/48	72	54/55	98	>25 ng/ml	23
6/13	46	24/27	89	>7.5 ng/ml	24,25
6/16	38	22/27	79	>16 ng/ml	26
25/38	68	34/39	87	>13 ng/ml	27

use occurred as many as 12 weeks before the clinically detectable reaction (22).

There is good reason to start retreatment if rising values of serial NSE measurements indicate a relapse (22,29).

NSE seems to be related both to the presence of parenchymal metastases and meningeal metastases. Plasma NSE has in one series been found to be related to CNS metastases in patients also suffering from other types of lung cancer (30). This could point to the possible use of NSE in the management of intracranial metastases in patients with histological types other than SCCL. In non-SCCL the tumor does not produce NSE, and an elevated plasma NSE concentration must be due to NSE coming from brain tissue. In SCCL patients it could, however, come from tumor tissue elsewhere in the body.

HORMONES

Calcitonin

Calcitonin as a marker for bronchogenic carcinoma was described by Gropp. In 45% of patients with SCCL and 17% of squamous cell carcinoma significantly elevated calcitonin levels (>180 pg/ml) were found. They could not detect any correlation between the calcitonin level and the degree of spread of the disease, but, during cytostatic treatment, a correlation between hormonal levels and the clinical course of the disease was observed. Response to therapy led to an equivalent fall in serum calcitonin for 1–2 months (31).

The frequency of elevated serum calcitonin before treatment has been determined in several studies (32–39).

The concentration of serum calcitonin was found to be elevated in around 60% of 475 patients. The incidence varies from 25% to 76%, which may be explained by random error, patient selection and the assays used (Table 4). Elevated concentrations of calcitonin are rare in other types of lung cancer (35,36).

TABLE 4. Incidence of elevated serum calcitonin in untreated patients with SCCL

%	No. of patients	Reference
70	70	32
51	54	33
64	74	34
56	135	35
75	28	36
25	40	37
76	24	38
26	50	39

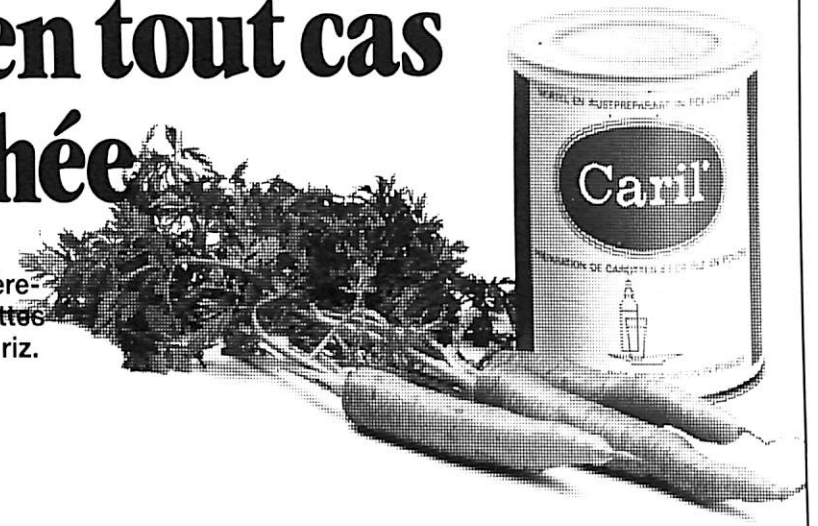
ACTH

Compared to calcitonin, adrenocorticotrophic hormone (ACTH) concentrations were elevated on average in only 27% of 252 patients with SCCL. The majority of cases, shown in Table 5, had only slightly elevated values, but in the other histological types of lung carcinoma no elevated concentrations were found (34,40–44).

In a further investigation, 18 hormonal polypeptides and amino-metabolites were measured in SCCL. In 65% of all patients, elevated serum calcitonin and in 29% elevated plasma ACTH were found. Serial measurements of ACTH and calcitonin showed that these hormones might additionally be useful in monitoring therapy in bronchogenic carcinoma patients. No relation between hormone levels

Caril®

traitement thérapeutique naturel en tout cas de diarrhée



Caril est une préparation entièrement naturelle à base de carottes sélectionnées et d'amidon de riz.

VENDU EXCLUSIVEMENT EN PHARMACIE

diadal b-1890 opwijk
tel.: 052/35.70.24
INTECOPHARM S.A.
LUXEMBOURG – Téléphone 48 58 76

Gastrosil® Tropfen

Gastrosil® 50 Injektionslösung – Gastrosil® Ampullen

Gastrosil®-Zäpfchen für Kinder und Erwachsene

Gastrosil® Tabletten – Gastrosil®-retard Kapseln

neu: Gastrosil®-retard mite Kapseln

so oder so: Gastrosil®

Das Metoclopramid-Programm

rezeptpflichtig

Zusammensetzung: Gastrosil: 1 Tablette enthält Metoclopramidhydrochlorid-Monohydrat 10,54 mg (≙ 10 mg Metoclopramidhydrochlorid). 1 ml Lösung (≙ 17 Tropfen) enthält Metoclopramidhydrochlorid-Monohydrat 5,97 mg (≙ 5,67 mg Metoclopramidhydrochlorid). 1 Zapfchen für Erwachsene enthält Metoclopramid 20 mg, Polidocanol 20 mg. 1 Zäpfchen für Kinder enthält Metoclopramid 10 mg, Polidocanol 10 mg. Gastrosil Injektionslösung: 1 Ampulle (2 ml) enthält 10 mg Metoclopramidhydrochlorid. Gastrosil 50 Injektionslösung: 1 Ampulle (10 mg) enthält 50 mg Metoclopramidhydrochlorid. Gastrosil retard: 1 Retardkapsel enthält 31,6 mg Metoclopramidhydrochlorid-Monohydrat (≙ 30 mg Metoclopramidhydrochlorid). Gastrosil retard mite: 1 Retardkapsel enthält 15,8 mg Metoclopramidhydrochlorid-Monohydrat (≙ 15 mg Metoclopramidhydrochlorid). Indikationen: Gastrosil, Gastrosil retard, Gastrosil retard mite: Motilitätsstörungen im oberen Magen-Darm-Bereich, z. B. bei Refluxkrankheit, Magenschleimhautentzündung, Sodbrennen. Zur unterstützenden symptomatischen Behandlung bei Magen- und Zwölffingerdarmgeschwüren, Übelkeit und Erbrechen bei Leber- und Nierenerkrankungen, Schädel- bzw. Hirnverletzungen, Reisekrankheiten, Migräne, medikamentenbedingte Übelkeit. Bei anhaltendem Schluckauf ist ein Therapieversuch angezeigt. Zusätzlich für Gastrosil retard mite: diabetische Gastroparese. Kontraindikationen: Phäochromozytom, prolactinabhängige Karzinome. Bei Epileptikern und Patienten mit extrapyramidalmotorischen Störungen wird Gastrosil nicht empfohlen. Patienten mit Sorbit-(Fructose)-Intoleranz, z. B. bei Fructose-1,6-Diphosphatasemangel, nicht mit Gastrosil Tropfen behandeln. Säuglinge und Kleinkinder sind von der Behandlung mit Gastrosil ausgeschlossen. Kinder von 8-14 Jahren, Schwangere und stillende Mütter sollten Gastrosil nur bei strenger Indikationsstellung einnehmen. Nebenwirkungen: In Einzelfällen kann nach Einnahme von Gastrosil ein dyskinetisches Syndrom (Krampfe im Gesichts-, Hals- und Schulterbereich) auftreten. Diese Erscheinungen klingen nach Absetzen des Präparates innerhalb einiger Stunden ab. I.v. Injektion von Akineton® (Wz. Knoll AG, Angaben des Herstellers beachten) bringt die Krampferscheinungen sofort zum Abklingen. Gelegentlich kann es zu Unruhezuständen, Müdigkeit, Schwindel, Kopfschmerzen, verstärkter Darmtätigkeit, Erhöhung des Prolaktinspiegels im Serum, Milchabsonderung und Brustdrüsenschwellung kommen. Nach Absetzen von Gastrosil verschwinden diese Nebenwirkungen vollständig innerhalb kurzer Zeit. Bei Langzeitanwendung kann es zu Menstruationsstörungen kommen. Gastrosil kann auch bei bestimmungsgemäßem Gebrauch das Reaktionsvermögen soweit verändern, daß die Fähigkeit zur aktiven Teilnahme am Straßenverkehr oder zum Bedienen von Maschinen beeinträchtigt wird. Dies gilt in verstärktem Maße im Zusammenwirken mit Alkohol. Wechselwirkungen mit anderen Mitteln: Bei gleichzeitiger Einnahme von Neuroleptika (zentral und peripher dämpfende Arzneimittel, z. B. Phenothiazine) können verstärkt krampfartige Beschwerden auftreten. Anticholinergika können die Wirkung von Gastrosil einschränken. Die Wirkung von trizyklischen Antidepressiva, Monoaminoxydase-Hemmern, Sympathikomimetika und Cimetidin kann beeinflußt werden. Die Aufnahme von Digoxin aus dem Darm kann vermindert, die Aufnahme von Paracetamol und verschiedene Antibiotika (z. B. Tetracycline) sowie von Alkohol kann beschleunigt werden.

Darreichungsformen und Packungsgrößen: Gastrosil: Packung mit 20 Tabletten, 50 Tabletten, 100 Tabletten, 20 ml Tropfen, 50 ml Tropfen, 100 ml Tropfen, 5 Zäpfchen für Kinder, 5 Zäpfchen für Erwachsene, 5 Ampullen. Gastrosil retard: Packung mit 10 Retardkapseln, 20 Retardkapseln, 50 Retardkapseln. Gastrosil retard mite: Packung mit 10 Retardkapseln, Packung mit 20 Retardkapseln, Packung mit 50 Retardkapseln, Anstaltspackungen.

HEUMANN PHARMA GMBH & CO · D-8500 NÜRNBERG

Littérature et échantillons: Comptoir Pharmaceutique Luxembourgeois S.A., Luxembourg

Stand: Januar 1986

HEUMANN PHARMA

TABLE 5. Incidence of elevated plasma concentrations of ACTH in untreated patients with SCCL

%	No. of patients	Reference
29	75	34
18	50	39
30	50	41
24	63	42
25	32	43

and the clinical stage of the disease could be proved (34,41).

It has been proposed that SCCL patients with ectopic hormone production were more inclined to develop metastases (45). This hypothesis was examined in 104 patients, measuring plasma ACTH, and in 86 patients measuring (inappropriate) ADH secretion for SIADH diagnosis. After 5 years observation no significant difference in the propensity to develop CNS metastases has been detected between patients with and without increased plasma levels of the hormones (15).

A number of other peptides have been investigated. None of these appear to contribute significantly to the clinical value of hormones in patients with SCCL (34,46–48).

ADH

About 20 years ago an association between endocrine syndrome and SCCL was documented. This tumor is able to produce ACTH as well as anti-diuretic hormone (ADH). Ectopic ADH secretion may be clinically manifested as inappropriate ADH secretion (SIADH). It can be demonstrated in about 8% of patients with SCCL (49,50).

The relation between ACTH syndrome and SIADH to SCCL is worth discussing, but the frequency is low in a series of patients (Table 7) (45,51–56).

The interpretation of the results for individual patients is difficult, and it should be mentioned that SIADH may occur in several non-malignant disorders, some of which may be secondary to the malignant disease.

Therefore, ACTH and ADH seem not to be useful parameters in monitoring therapy or predicting relapse.

THE PROTEIN β-2-MICROGLOBULIN

Höllgren measured β-2-microglobulin (β2-m) in 467 patients with mainly suspected pulmonary malignancy and found that patients who had low circulating levels of β2-m at remission (less than 1.5 mg/l) had a 'better prognosis' than those with serum levels greater than 3.0 mg/l. (57).

TABLE 6. Peptide hormones in untreated patients with SCCL

	%	No. of patients	Reference
Parathormone	33	57	34
Parathormone	27	43	46
Insulin	5	65	34
Gastrin	20	69	34
Glucagon	11	46	34
Secretin	0	46	34
Growth hormone	9	46	34
α-MSH	19	43	46
β-Endorphin	45	58	46
Oxytocin	30	61	47
ADH-neurophysin	65	103	47
LPH	54	24	48

TABLE 7. Incidence of endocrine syndromes in SCCL in %

ACTH syndrome	SIADH	No. of patients	Reference
5	10	84	45
3	5	39	51
2	11	106	52
-	7	250	53
1	1	75	54
5	2	42	55
-	11	350	56

Very promising results were published concerning β2-m measurement using the 'modifying activity' of β2-m. Elevated values of β2-m (greater than 0.30 arbitary units) have been demonstrated in 49 of 54 patients with SCCL. Relapse was accompanied by rising values in 11 of 15 patients monitored during chemotherapy. In 9 of these patients abnormally high values of β2-m were demonstrated more than 1 month before clinical or radiological evidence of progression. The estimation of β2-m modifying reactivity provides relevant clinical information, but it is too laborious for routine clinical application (58).

In contrast, other findings show that high levels of β2-m in lung cancer patients were rare and still within the range of non-malignant diseases (17).

PROSTAGLANDINS AND OTHER FACTORS

Fiedler proved that prostaglandin E_2 (PGE_2) and 13,14-dihydro-15-keto-prostaglandin F_2 (DHK-PGF_2) are significantly elevated in lung tumor patients before surgery. The concentration decreased postoperatively. It can be demonstrated that PGF_2 and DHK-PGF_2 are almost completely normalised within 1 hour after the last ligature of tumor vessels. In this interesting new field, clinical consequences can be established after lengthy follow-up (59).

Many investigations are trying to find new markers for lung cancer—the following survey is given (Table 8). Tumor markers which have been found in the literature and which show some elevated serum concentrations in lung

TABLE 8. Tumor markers indicating some usefulness in lung cancer patients

Marker	Histology	Reference
LDH	SCCL	60
Fucosyl transferase	SCCL, squamous	61
Sialyltransferase	SCCL, squamous	61
α-1 acid glycoprotein	SCCL	6,62
α-2 pregn.ass. glycoprot.	Bronchus	63,64
Ferritin	Bronchus	6,17,65
TPA	Bronchus	66
Zinc	Squamous	67
HLA B8 antigen	Bronchus	68
HTAA	Squamous	69
Bombesin	SCCL	70,71

cancer patients, and those giving any indication of possible effective use in the future are included. The clinical usefulness of these observations either prognostically or diagnostically can be judged only after further investigations and studies.

IMMUNOGLOBULINS

It has to be stated that the measurement of serum immunoglobulins (IgG, IgM, IgA) is not helpful in the follow-up of lung cancer patients (72).

MARKER PANELS

As no single marker is significantly elevated in the majority of patients with SCCL, the use of marker panels has been examined by several investigators. In this way the incidence of elevated markers is about 20% higher than with a single marker (15,37,41,54,73).

Havemann measured calcitonin, ACTH and CEA monthly before and during treatment in 250 patients with SCCL. In 80% of the patients a correlation between calcitonin plus CEA and X-rays was found. The examinations were disappointing with regard to detection of early relapses (74).

CONCLUSION

It is suggested that the use of serial measurements of NSE, CEA and calcitonin are useful in clinical follow-up in SCCL. In most patients elevated pretreatment levels decrease with tumor regression and increase at relapse.

In adenocarcinomas CEA seems to be of some interest for diagnosis and prognosis.

A correlation between fucosyl- and sialyltransferase and sqamous cell carcinoma was seen, but further investigations are necessary to confirm these results.

REFERENCES

1. BATES S. E. and LONGO D. L.: Tumor markers: value and limitations in the management of cancer patients. Cancer Treat. Rev. 12; 163, 1985.
2. KARRER K., DENCK H., KARNICKA-MLODKOWSKA H., DRINGS P., ERZEN J., SUN Y., THERMAN M., BERKARDS B., LIAO M., DELL'AMORE D. and ROTHMUND J.: Combined modality treatment after surgery for cure for small cell bronchial carcinoma at TNM-stage I, in SALMON A. (ed.): Adjuvant Therapy of Cancer V., pp. 189-199, London, Grune & Stratton, 1987.
3. GOLD P. and FREEDMAN S. O.: Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. J. exp. Med. 121, 439-462, 1965.
4. ROGERS G. T.: Carcinoembryonic antigens and related glycoproteins molecular aspects and specificity. Biochem. biophys. Acta 695, 227-249, 1983.
5. LO GERFO P., HERTER F. P., BRAUN J. and HANSEN H. T.: Tumor associated antigen with pulmonary neoplasms. Ann. Surg. 175, 495-500, 1982.
6. GROPP C., LEHMANN F. G., BAUER H. W. and HAVEMANN K.: Carcinoembryonic antigen, α1-fetoprotein ferritin and α2-pregnancy associated glycoprotein in the serum of lung cancer patients and its demonstration in lung tumor tissues. Oncology 34, 267-272, 1977.
7. COOMBES R. C., ELLISON M. L. and NEVILLE A. M.: Biochemical markers in bronchogenic carcinoma. Br. J. Dis. Chest. 72, 263-287, 1978.
8. DENT P. B., McCULLOCH P. B., WESLEY-JAMES O., MACLAREN R., MUIRHEAD W. and DUNNETT C. W.: Measurement of carcinoembryonic antigen in patients with bronchogenic carcinoma. Cancer 42, 1484-1491, 1978.
9. CONCANON J. P.: Evaluation of the clinical significance of carcinoebryonic antigen (CEA) plasma levels in patients with bronchogenic carcinoma. World Conference on Lung Cancer 10–13 May, South Carolina, U.S.A., 1978.
10. CANIVET B., LALANNE C. M., KREBS B. P., AUBANEL J. M., and BLAIVE B.: Carcinoembryonic antigen and cancer of the lung: two-way determination. Tumor Diagnost. 4, 203-207, 1980.

11. VINCENT R. G., CHU T. M. and LANE W. W.: The value of carcinoembryonic antigen in patients with carcinoma of the lung. Cancer 44, 85, 1979.

12. LABERGE F., FRITSCHE H. A., UMSAWASDI T., CARR D. I., WELCH S., MURPHY W. K., CHIUTEN D. E., DHINGRA H. M., FARHA P., SPITZER and VALDEVIVIESO M.: Use of carcinoembryonic antigen in small cell lung cancer. Cancer 59, 2048, 1987.

13. DENT P. B., LOUIS J. A., McCULLOCH P. B., DUNNETT C. W. and CEROTTINI J. C.: Correlation of elevated C1q binding activity and carcinoembryonic antigen levels with clinical features and prognosis in bronchogenic carcinoma. Cancer 45, 130-136, 1980.

14. FORD C. H. T., STOKES H. J. and NEWMAN C. E.: Carcinoembryonic antigen and prognosis after radical surgery for lung cancer: immunocytochemical localization and serum levels. Br. J. Cancer 44, 145-153, 1981.

15. HANSEN M. and PEDERSON A. G.: Tumor markers in patients with lung cancer, 4th World Conference on Lung Cancer (IASLC), Toronto, Canada, August 1985.

16. JAESCHOCK R. R., IRLICH G. and PALOMBA P.: Die Wertigkeit der CEA-Bestimmung beim Bronchialkarzinom. Krebsgeschehen 13, 1-5, 1981.

17. MAXIM P. E., VELTRI R. W. and SPRINKLE P. M.: Soluble tumor-associated markers in lung cancer extracts. Oncology 38, 147-153, 1981.

18. GOSLIN R. H., SKARIN A. T. and ZAMCHECK N.: Carcinoembryonic antigen. J. Am. Med. Ass. 246, 2173, 1981

19. HAVEMANN K., HOLLE F. and GROPP C.: Prospective multicenter study of hormone markers in small cell lung cancer, in HAVEMAN K., SORENSON G. and GROPP C. (eds): Peptide Hormones in Lung Cancer, vol. 99, p. 194. Berlin, Springer, 1985.

20. TAPAI F. J., POLAK J. M. and BARBOSA A. J. A.: Neuron specific enolase is produced by neuroendocrine tumors. Lancet 1, 808-811, 1981.

21. CARNEY D. N., IHDE D. C., COHEN M. H., MARANGOS P. I., BUNN, R. A. Jr. and MINNA, J. D.: Serum neuron-specific enolase: a marker for disease extent and response to therapy of small cell lung cancer. Lancet 1, 583-585, 1982.

22. JOHNSON D. H., MARANGOS P. J., FORBES J. T., HAINSWORTH, J. D., WELCH VAN R. and HANDE K. R.: Potential utility of serum neuron-specific enolase levels in small cell carcinoma of the lung. Cancer Res. 44, 5409, 1984.

23. ESCHER T., STEINHOLTZ L., BERGH J., NÖU E., NILSSON K. and PAHLMAN S.: Neurone specific enolase: a useful diagnostic serum marker for small cell carcinoma of the lung. Thorax 40, 85-90, 1985.

24. ARIYOSHI Y.: Evaluation of neuron-specific enolase as a new tumor marker for carcinoma of the lung. Gan No Rinsko 30, 569, 1984.

25. ARIYOSHI Y., KATO K., ISHIGURO Y., OTA K., SATO T. and SUCIH T.: Evaluation of serum neuron-specific enolase as a tumor marker for carcinoma of the lung. Gann 74, 219-225, 1983.

26. AKOUN G. M., SCARNA H. M., MILLERON B. H., BENICHONN M. R. and HERMAN D. P.: Serum neuron-specific enolase. A marker for disease extend and response to therapy for small cell lung cancer. Chest 87, 39, 1985.

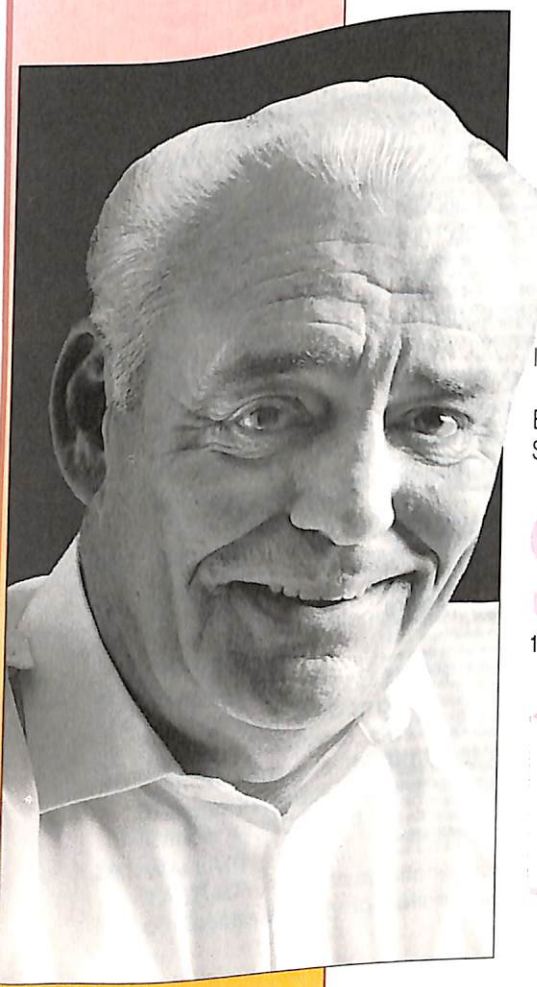
27. COOPER E. H., SPLINTER T. A. W., BROWN D. A., MUERS M. F., PEAKE M. D. and PEARSON S. L.: Evaluation of a radioimmunoassay for neuron specific enolase in small cell lung cancer. Br, J. Cancer 52, 333-338, 1985.

28. ADEWOLE I. F. and NEWLANDS E. S.: Neuron specific enolase (NSE) as a tumor marker and comparative evaluation with carcinoembryonic antigen in small cell lung cancer. Med. Oncol. Tumor Pharmacother 4, 11, 1987.

29. KARRER K., WOROFKA B., ULSPERGER E. and TILSCHER I.: The role of tumor mar-

L'APPROCHE SAINE

de l'hypertension artérielle lorsque les vaisseaux sanguins ne sont plus de la première jeunesse



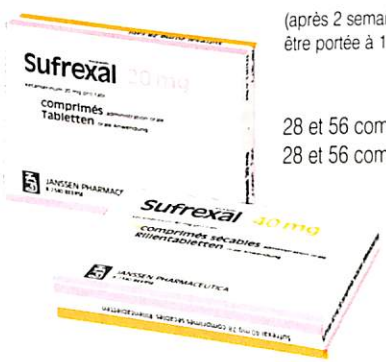
Cela ne va pas de soi, car une baisse de la tension s'accompagne malheureusement souvent d'une baisse de l'irrigation...
Ce qui n'est pas une bonne chose.
Surtout lorsque les vaisseaux sanguins ont un certain âge.

Désormais, il existe une solution: le blocage de la sérotonine 2 périphérique — ou simplement blocage S_2. L'excitation par la sérotonine des récepteurs S_2 périphériques augmente la résistance périphérique et favorise l'agrégation plaquettaire. L'inhibition par un antagoniste S_2 des mêmes récepteurs diminue la résistance périphérique et arrête l'agrégation plaquettaire.
La baisse de tension ne s'accompagnera donc plus d'une baisse de l'irrigation, laquelle sera au contraire intensifiée.

Et c'est une bonne chose.
Surtout pour des vaisseaux qui ne sont plus tout jeunes.

Sufrexal

1 comprimé à 20 mg, 2 x par jour ANTAGONISTE S_2 PERIPHERIQUE



(après 2 semaines au plus tôt, la dose peut éventuellement être portée à 1 comprimé à 40 mg, 2 x par jour)

28 et 56 comprimés à 20 mg de kétansérine
28 et 56 comprimés à 40 mg de kétansérine

BONNE NOUVELLE POUR LES 60+

JANSSEN PHARMACEUTICA

la grandeur dans la recherche

2340 Beerse

Sufrexal

TRADEMARK

Composition: Comprimés: - 20 mg de kétansérine (= 27,6 mg de tartrate de kétansérine (R 49 945)) par comprimé. - 40 mg de kétansérine (= 55,2 mg de tartrate de kétansérine (R 49 945)) par comprimé. **Ampoules:** - 10 mg de kétansérine (= 13,8 mg de tartrate de kétansérine (R 49 945)) par ampoule de 2 ml (5 mg/ml). - 50 mg de kétansérine (= 69 mg de tartrate de kétansérine (R 49 945)) par ampoule de 10 ml (5 mg/ml). **Formes, voies d'administration et conditionnements: Comprimés pour** administration orale: Comprimés à 20 mg: emballage alvéolé de 28 ou 56 comprimés. Comprimés à 40 mg: emballage alvéolé de 28 ou 56 comprimés sécables. **Ampoules pour** injection intraveineuse ou intramusculaire: Boîte de 5 ampoules de 2 ml. Boîte de 5 ampoules de 10 ml. **Indications:** 1. Administration chronique: Sufrexal est indiqué dans le traitement chronique, chez l'adulte, de l'hypertension essentielle et rénale légère, modérée ou grave, en monothérapie ou en association avec des diurétiques ou des β-bloquants. 2. Administration aiguë: Sufrexal est indiqué dans le traitement aigu de l'hypertension, telle que l'hypertension per- et postopératoire, la prééclampsie, etc. Sufrexal convient au traitement de l'hypertension chez tous les patients, y compris les patients âgés, les patients avec insuffisance cardiaque, diabète sucré, asthme ou troubles circulatoires périphériques. **Posologie et mode d'emploi:** 1. Traitement oral: La dose initiale est de 20 mg deux fois par jour (aussi bien en monothérapie qu'en association avec d'autres antihypertensifs). Sufrexal exerce son activité progressivement, de sorte que la baisse maximale de tension artérielle est atteinte après 2 à 3 mois. Certaines personnes ont besoin d'une dose double. On ne peut doubler la dose qu'après 2 semaines au plus tôt si la dose initiale n'a pas eu d'effet. • Si, après 2 à 3 mois de monothérapie par Sufrexal, la tension artérielle n'est pas complètement maîtrisée, une association avec d'autres antihypertensifs, tels que diurétiques ou β-bloquants, peut renforcer l'effet antihypertensif de Sufrexal. • Sufrexal peut être pris pendant les repas ou en dehors de ceux-ci. • Des doses de plus de 40 mg par prise sont à déconseiller. Elles n'augmentent pas l'effet antihypertensif de Sufrexal et sont moins bien tolérées. • Les patients âgés et les patients avec insuffisance rénale peuvent être traités par les doses normales de Sufrexal. Chez les patients ayant une insuffisance hépatocellulaire grave, une dose supérieure à 2 x 20 mg par jour est à déconseiller. • Sufrexal n'est pas éliminé par l'hémodialyse. • Le traitement par Sufrexal ne doit pas être interrompu en cas d'intervention chirurgicale. 2. Traitement parentéral: La dose thérapeutique normale doit être déterminée individuellement et peut varier, chez les adultes, de 5 à 30 mg par administration. *a) voie intraveineuse:* - soit en injection unique: on peut injecter jusque 5 mg (1 ml) en une fois (en 10 sec.). Si nécessaire, l'administration peut être répétée, avec chaque fois un intervalle de quelques minutes, jusqu'à un maximum de 30 mg; - soit en perfusion rapide: 3 mg par minute jusqu'à ce que la tension artérielle soit maîtrisée, avec un maximum de 30 mg; - la dose maximale par 24 heures est de 150 mg (perfusion + injection en bolus). • L'effet thérapeutique est généralement obtenu une à deux minutes après administration de la dose intraveineuse adaptée. • L'effet d'une administration intraveineuse unique est le plus souvent de courte durée (30 à 60 minutes) et peut être entretenu par une perfusion de 2 à 6 mg par heure (35 à 100 μg par minute). On ne peut procéder à une perfusion qu'après une injection préalable (bolus). *b) voie intramusculaire:* 10 mg (2 ml), à répéter si nécessaire après 15 à 30 minutes, avec un maximum de 30 mg. **Contre-indications:** Il n'y a pas de contre-indications connues. **Effets indésirables:** Au début du traitement, une sensation de vide dans la tête peut survenir chez certains patients — le plus souvent jeunes. Cet effet secondaire est peu prononcé, il apparaît 1 à 2 heures après l'administration et disparaît le plus souvent spontanément après quelques jours quand on poursuit le traitement. Occasionnellement, de la céphalée, des vertiges, de la fatigue, de la sécheresse de la bouche et de l'intolérance gastrique ont été mentionnés. Ces effets secondaires ont cependant également été observés chez des patients sous placebo dans des études avec contrôle placebo. Chez quelques patients, une formation d'œdème pendant le traitement par Sufrexal a été signalée. Sufrexal est bien toléré, surtout par les patients âgés. Les paramètres biochimiques et hématologiques ne sont pas influencés négativement lors d'un traitement prolongé par Sufrexal. Bien qu'on n'ait pas rapporté de réactions hépatiques au cours d'un traitement par Sufrexal, de pareilles réactions sont possibles avec tout médicament qui est métabolisé dans le foie. L'hypotension, y compris l'hypotension orthostatique, est très rare. Chez quelques patients prédisposés (notamment sous diurétiques éliminant le potassium, sous antiarythmiques allongeant l'espace QT, ou présentant un bloc auriculo-ventriculaire du 2e ou 3e degré), des arythmies ventriculaires réversibles (de type "torsade de pointes") ont été constatées lors d'un traitement oral chronique par Sufrexal. **Interactions:** Interactions désirées: Les études des associations de Sufrexal à des diurétiques et à des β-bloquants mettent en évidence une activité antihypertensive additionnelle. Interactions indésirables: Lorsque des antiacides sont utilisés simultanément, l'absorption de Sufrexal peut être diminuée. C'est pourquoi il est recommandé de prendre les antiacides éventuels 1 à 2 heures après Sufrexal (voir aussi rubrique "Précautions particulières"). Jusqu'à présent, on n'a pas constaté d'interactions avec les anticoagulants, les hypoglycémiants ou les dérivés de la digitaline. Bien que cela n'ait pas été démontré, l'administration simultanée de médicaments anti-inflammatoires non stéroïdes pourrait théoriquement diminuer l'effet antihypertensif de Sufrexal. Pour éviter l'administration de Sufrexal en cas d'hypokaliémie, il faut si Sufrexal est associé à un diurétique, toujours inclure un diurétique d'épargne potassique dans le schéma thérapeutique, que ce soit ou non avec un autre diurétique. Sufrexal ne peut alors être associé à un diurétique éliminant le potassium que si un diurétique d'épargne potassique est inclus en même temps dans le schéma thérapeutique. En cas d'utilisation chronique de corticoïdes et de laxatifs, il est conseillé de contrôler régulièrement le taux de potassium dans le sang.

kers for the indication to cancer chemotherapy for minimal residual disease. Path. Clin. 1, 17, 1986.

30. ARONY R. S., DERMODY W. C. and ALDENDORFER P.: Multiple sequential biomarkers in monitoring patients with carcinoma of the lung. Cancer Treat. Rep. 68, 859–866, 1984.
31. GROPP C., HAVEMANN K. and SCHEUER A.: Ectopic hormones in lung cancer patients at diagnosis and during therapy. Cancer 46, 347-354, 1980.
32. BIERBAUM W., HUTOMA T. and NIEDERLE N.: Calcitonin in monitoring patients with small cell carcinoma of the lung during chemotherapy. Cancer Detect. Prev. 5, 258, 1982.
33. GRECO F. A., SISMANI A. and HANDE K.: Plasma calcitonin and andidiuretic hormone (ADH) as markers in small cell lung cancer. Proc. Am. Ass. Cancer Res. 22, 342, 1981.
34. HANSEN M., HANSEN H. H., HIRSCH F. R., ARENDS J., CHRISTENSON J. D., CHRISTENSEN J. M., HUMMER and KÜHL C.: Hormonal polypeptides and amine metabolites in small cell carcinoma of the lung, with special reference to stage and subtypes. Cancer 45, 1432-1437, 1980.
35. LUSTER W., GROPP and SOSTMANN H.: Demonstration of immunoreactive calcitonin in sera and tissues of lung cancer patients. Eur. J. Cancer clin. Oncol. 18, 1275-1283, 1982.
36. McKENZIE C. G., EVANS I. M. A., HILLYARD C. I., HILL P., CARTER S., TAN M. K. and MACINTYRE I.: Biochemical markers in bronchial carcinoma. Br. J. Cancer 36, 700-707, 1977.
37. SAPPINO A. P., ELLISON M. L. and CARTER S. C.: Correlation of 3 tumour markers (calcitonin, CEA and beta-hCG) with response to therapy and extent of disease in small cell lung cancer. Br. J. Cancer 44, 300, 1981.
38. WALLACH S. R., ROYSTON I. and TAETLE R.: Plasma calcitonin as a marker of disease activity in patients with small cell carcinoma of the lung. J. clin. Endocrin. Metab. 53, 602-606, 1981.
39. YAMAGUCHI K., KAORU A., ADACHI I., OTSUBOTO K., NAGASAKI B. S., SUZUKI M. and MARUNO K.: Peptide hormone production in small cell lung carcinomas with particular reference to gastrin-releasing peptide. Jap. J. clin. Oncol. 16, 235, 1986.
40. DAVIS S. and MAY P. B.: Infrequent elevation of plasma ACTH in patients with bronchogenic carcinoma. Am. J. med. Sci. 283, 2-7, 1982.
41. GROPP C., HAVEMANN K. and SCHEUER A.: Ectopic hormones in lung cancer patients at diagnosis and during therapy. Cancer 46, 347-354, 1980.
42. RATCLIFFE J. G., PODMOSE J. and STACK B. H.: Circulating ACTH and related peptides in lung cancer. Br. J. Cancer 45, 230-236, 1982.
43. SPAULDING M. B., PEDERSON R. and FOLTS J.: A comparison of immunoreactive gamma MSH and ACTH in monitoring carcinoma of the lung. Proc. Am. Soc. clin. Oncol. 2, C-25, 1983.
44. TORSTENSSON S., THORÉU and HALL K.: Plasma ACTH in patients with bronchogenic carcinoma. Acta Med. scand. 207, 353-357, 1980.
45. LOKICH J. J.: The frequency and clinical biology of the ectopic hormone syndromes of small cell carcinoma. Cancer 50, 2111-2214, 1982.
46. GROPP C., LUSTER W., HAVEMANN K. and LEHMANN F. G.: ACTH, calcitonin, alfa-MSH, beta-endorphin, parathormone and beta-hCG in sera of patients with lung cancer, in UHLENBRUCK G. and WINTZER G. (eds): CEA und andere Tumormarker, pp. 358-363. Leonberg, Tumor Diagnostic, 1981.
47. NORTH W. G., MAURER H., VALTIN H. and O'DOMELL J. F.: Human neurophysins as potential tumor markers for small cell carcinoma of the lung: application of specific radioimmunoassays. J. clin. Endocrin. Metab. 51, 892-897, 1980.

48. ODELL W. D., WOLFSEN A. R., BACHELOT J. and HIROSE F. M.: Ectopic production of lipotropin by cancer. Am. J. Med. 66, 631-638, 1979.

49. PADFIELD P. L., MORTON J. J., BROWN J. J., LEVER A. E., ROBERTSON J. I. S., WOOD M. and FOX R.: Plasma arginine vasopressin in the syndrome of antidiuretic hormone excess associated with bronchogenic carcinoma. Am. J. Med. 61, 825, 1976.

50. RICHARDSON R. I., GRECO F. A., OLDHAM R. K. and LIDDLE G. W.: Tumor products and potential markers in small cell lung cancer. Sem. Oncol. 5, 253, 1978.

51. AZZOPARDI J. G., FREEMAN E. and POOLE G.: Endocrine and metabolic disorders in bronchial carcinoma. Br. Med. J. 4, 528-529, 1970.

52. BONDY, P. K. and GILBY, E. D.: Endocrine function in small cell undifferentiated carcinoma of the lung. Cancer 50, 2147-2153, 1982.

53. HAINSWORTH J. D., WORKAMNN R. and GRECO F. A.: Management of the syndrome of inappropriate antidiuretic hormone secretion in small cell lung cancer. Cancer 51, 161-165, 1983.

54. HANSEN M., HAMMER M. and HUMMER L.: Diagnostic and therapeutic implications of ectopic hormone production in small cell carcinoma of the lung. Thorax 35, 101-106, 1980.

55. RASSAN J. W. and ANDERSON G.: Incidence of paramalignant disorders in bronchogenic carcinoma. Thorax 30, 86-90, 1975.

56. LIST A. F., HAINSWORTH J. D., DAVIS B. W., HANDE K. R., GRECO A. and JOHNSON D. H.: The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in small-cell lung cancer. J. clin. Oncol. 4, 1191, 1986.

57. HÄLLGREN R., NOU E. and LUNDQVIST G.: Serum β2-microglobulin in patients with bronchial carcinoma and controls. Cancer 45, 780-785, 1980.

58. NISSEN M. H., PLESNER T. and ROTH M.: Modification of beta 2-microglobulin in serum from patients with small cell bronchial carcinoma of the lung. Correlation with clinical course. Clin. Chim. Acta 141, 41-50, 1980.

59. FIEDLER L., SCHLEGEL G., KAISER D. and ZAHRADNIK H. P.: Untersuchungen zum perioperativen Verhalten von Prostaglandin Es (PGE2) und 13,14-dihyrdo-15-keto-PGF2 (DHK-PGF2) im Serum beim Bronchial-karzinom. Onkologie 2, 108-112, 1979.

60. DOLL D. C.: Serum lactic dehydrogenase (LDH) and bone marrow involvement in small cell carcinoma of the lung (SCCL). Proceedings of ASCO 4, C-23, 19-21 May, 1985, Houston, TX.

61. RONQUIST G. and NOU E.: Serum sialyltransferase and fucosyltransferase activities in patients with bronchial carcinoma. Cancer 52, 1679-1683, 1983.

62. GANZ P. A., BARAS M., YEUNG M. P. and ELASHOFF R. M.: Monitoring the therapy of lung cancer with α1-acid glycoprotein. Cancer Res. 44, 5415-5421, 1984.

63. BAUER H. W.: The pregnancy-associated α2-glycoprotein (α2-PAG) a tumour marker. Klin. Wschr 59, 149-155, 1981.

64. BRIESE V., SZABO D. G., THAN G. N., WILLROTH P. O. and STRAAUBE W.: Zum Verhalten einiger Tumormarker Orosomukid, schwangerschaftassoziertes α2-Glycoprotein, Schwangerschaftsprotein-1, plazental specific-tissue protein 10 im Serum von Patienten mit Bronchialkazrinom. Arch. Geschwul. 56, 13, 1986.

65. COX R., GYDE O. H. and LEYLAND M. T.: Serum ferritin in small cell lung cancer. Eur. J. Cancer clin. Oncol. 22, 831, 1986.

66. MUHRER K. H., BAUER T., GREBE S. F. and MÜLLER H.: Short- and long-term TPA monitoring in patients with gastrointestinal and bronchial carcinoma following radical or palliative tumor resection. Tumor Diag. Ther. 7, 120, 1986.

67. ISSELL B. F., MACFAYDEN B. F., GUM E. T., VALDIVIESO M., DUDRICK St. J. and

BODEY G. P.: Serum zinc levels in lung cancer patients. Cancer 47, 1845-1848, 1981.

68. SENGAR D. P. S., MCLEISH W. A., STEWART T. H. M. and HARRIS J. E.: HLA antigens bronchogenic carcinoma. Oncology 34, 143-145 1977.
69. KELLY B. S. and LEVY J. G.: Detection of tumour-associated antigens in human bronchogenic carcinoma by the enzyme-linked immunosorbent assay (ELISA). Br. J. Cancer 41, 388-398, 1980.
70. SORENSON G. D., BLOOM S. R. and GHATEI M. A.: Bombesin production by human small cell carcinoma of the lung. Regul. Rep. 4, 59, 1982.
71. MOODY T. W., CARNEY D. N. CUTTITTA F., QUATTROCHI K. and MINNA J. D.: High affinity receptors for bombesin/GRP like peptides on human small cell lung cancer. Life Sci. 37, 105, 1985.
72. MICKSCHE M.: Immunologische Aspekte des Lungenkarzinoms, in DENCK H. and SIGHART H. (eds): Das Bronchuskarzinom heute, pp. 255-283. Vienna, Adolf Holzhausens Nfg, 1980.
73. BUCCERI G. F., BENEDETTO V., SARTORIS A. M., FERRIGNO D., CURCIO A. and VOLA F.: Clinical value of a multiple biomarker assay in patients with bronchogenic carcinoma. Cancer 57, 2389, 1986.
74. HAVEMANN K., HOLLE R. and GROPP C.: Prospective multicenter study of hormone markers in small cell lung cancer. Recent Res. Cancer Res. 99, 194-208, 1985.

Tumor Markers for the Diagnosis, Prognosis, Treatment and Follow-up of Gynaecological Tumors

E. Ulsperger and K. Karrer

Abstract

It would be of benefit for the clinical relevance of tumor marker determination to be demonstrated, as a lot of markers are now in clinical use.

Increased levels of carcinoembryonic antigen correlate with the stage of breast carcinoma. CA 15-3 should also be measured during follow-up of patients with this disease. The latest findings suggest a higher sensitivity and specificity of CA 15-3 than of CEA. The prognostic value and the usefulness of CEA measurement in screening seem to be poor.

The measurement of CA 125 seems to be a reliable method for monitoring the presence and clinical behavior of ovarian cancer. It is suggested that invasive diagnostic procedures are not required in patients with normal marker levels.

The management of chorion carcinoma can be determined as an ideal model in the range of marker application. Only in this disease does the marker HCG reach almost 100% sensitivity and specificity. The definition of response to chemotherapy and the appearance of relapse can be based on HCG measurement.

INTRODUCTION

Significant advances in the treatment of gynaecological tumors have been paralleled by the identification of various tumor markers. Many markers have been used indiscriminately. In general the clinical relevance of marker determination in specific carcinomas has to be proven. A survey of markers used for management of gynaecological neoplasms, including breast cancer, is given here.

During the last decades various researchers have tried to find, besides the clinical investigations such as scanning, computer tomography, X-ray and sonography, a reliable serum parameter which would be useful for the diagnosis, prognosis, follow up, therapy, detection (screening) and management of tumors. Such a marker should be produced only by the tumor cell and be

Institute for Epidemiology of Neoplasms, of the University of Vienna, Borschegasse 8a, A-1090 Vienna, Austria

detectable in body fluids. No measurable level should occur in benign diseases or healthy persons. A correlation between the level and the tumor bulk, as well as the effect of antineoplastic treatment, should also exist. No reliable marker has so far been detected.

None of the available markers can be defined as ideal, with the exception of β-HCG in trophoblastic malignancy, which has a sensitivity and specificity of almost 100% (Table 1).

If the therapy for a given malignancy is inadequate, it is of little clinical use and of no advantage for the patient to demonstrate an occult disease, a relapse or a disease progression by marker estimation.

TABLE 1.

Definitions
Sensitivity: percentage of patients with a malignant disease showing elevated marker levels—true positive values.
Specificity: percentage of patients without a malignant disease who have normal marker levels—true negative values.

The most commonly used tumor markers in gynaecological oncology which will be discussed are; for breast cancer: CEA (carcinoembryonic antigen), CA 15-3 (cancer antigen) and TPA (tissue polypeptide antigen); for ovarian carcinomas: CA 125 and CEA; and for carcinoma of the uterus: β-HCG (human chorionic gonadotropin).

BREAST CANCER

It is well known that the improved postoperative therapeutic management of breast cancer, including hormone-, chemo- and radiotherapy, has led to a better prognosis. These treatments are more effective when diagnosis is made as early as possible in case of relapse (1).

The 'sensitivity' of the most frequently used and most often discussed markers in the management of mammary carcinoma is given in Table 2 (2,3).

TABLE 2. Sensitivity of markers used in the clinical follow-up of breast cancer patients in all stages

	Günczler (2)	Hoffmann (3)
CEA	66%	50%
CA 15-3	76%	70%
TPA	—	80%

CEA

Carcinoembryonic antigen is a nonspecific marker which has been commonly used to monitor various malignant disorders. In current clinical practice, the CEA levels are used primarily to monitor the effect of treatment. CEA is the most frequently used and best documented marker for female breast cancer studies (4).

As there is only a certain percentage of malignant cells in any tumor which are able to express the marker, the pathological values are concordant with a greater tumor mass.

Patients may show a discordant behavior in marker levels and clinical findings during follow-up; raised or elevated marker levels might indicate an effective treatment and remission (5,6).

In breast cancer the incidence and level of CEA correlates with the stage of disease (Table 3) (2,4,7,8).

Several findings show that CEA levels are elevated more often and reach the highest levels in cases of liver and bone metastases, whereas they remain normal in most cases of local recurrence (2,9–11). In disease-free breast cancer patients, CEA determinations are useful only in lymph node positive patients. CEA is unable to predict a recurrence in lymph node negative patients (7,12).

The findings of Veronesi (12) indicate that gradually increasing elevations predict a relapse. Only highly elevated (greater than 20 ng/ml) and gradually increasing values could predict recurrence, with a median of 8 months (12,13).

Postoperative elevations and also, in some studies, preoperative elevations of CEA, corre-

TABLE 3. Comparison of sensitivity of CEA in localized and advanced breast cancer (%)

Localized	Advanced	Cut-off ng/ml	References
30	73	2.7 5 (smokers)	7
27–55	80	2.5	8
16.9	70.9	9	4
32	72	5	2

late with disease recurrence. In Mayer's investigations of postoperative breast cancer patients in stage I, II and III only 5% of patients with normal postoperative values compared to 16% with elevated postoperative CEA levels developed a relapse (7).

Using a cut-off level of 4 ng/ml for postoperatively elevated CEA levels concerning the risk of developing metastases in patients with stage I breast cancer, no prognostic use was found (4,12). However, patients with stage II and III disease, with elevated postoperative values, are associated with an increased risk of development of recurrent disease (7).

Response to therapy and disease progression concorded in 63% of cases with decreasing and increasing CEA values, respectively (5). However, there is no doubt that in a number of patients CEA elevation precedes the clinical signs of recurrent disease (8,6,11,14,15).

CEA is a marker which permits detection before other diagnostic means in more than 50% of relapses. But therapeutic consequences, without other clinical parameters, should only be drawn if there is a significant and persistent rise in the marker level.

CA 15-3

The glycoprotein cancer antigen 15-3 gained some importance, as its sensitivity as well as specificity in breast cancer are higher than those of CEA (3,16). As previously mentioned, CEA gains a sensitivity of about 65% and a specificity of 87%. Compared to these investigations, CA 15-3 shows a sensitivity of about 76% and a specificity of 93% (2). Tumor progression is indicated in 70% and remission in 60% of patients (3).

The advantage of CA 15-3 above CEA was also demonstrated through the investigations of Günzler and Hayes (Fig. 1). This shows the sensitivity of both markers depending on tumor stage, subdivided in localized disease and haematogenic metastasis (2,16).

During follow-up, an increasing CA 15-3 level indicates the end of the remission. In primarily

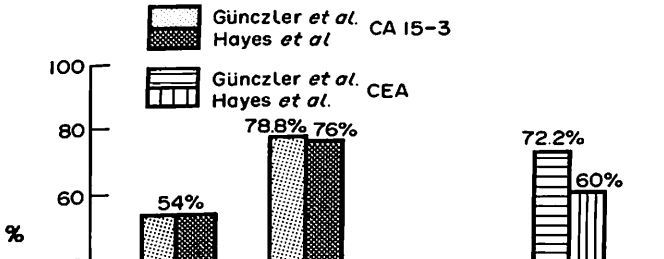


Fig. 1. Sensitivity depending on tumor stage. Cut-offs: CA 15-3, 30 U/ml; CEA 5 ng/ml.

operated patients, CA 15-3 elevations indicate metastatic disease (3). The combined measurement of CEA and CA 15-3 enlarges the sensitivity to 71%, or even to 98% (2,3,16,17).

TPA

TPA can be classified as an oncofoetal antigen. In 89% of metastatic breast cancer patients, the TPA measurements showed concordance with clinical results, compared to only 71% in CEA (18). Combining CEA with TPA the sensitivity was enlarged in patients with metastatic breast cancer; in patients without progression from 39% to 49% and in patients with progressive disease from 70 to 79% (6).

Hünermannn observed a sensitivity of 96% and a specificity of 99% in treated patients with metastatic breast cancer by combined measurement of CEA and TPA. The sensitivity for CEA was only 52% and for TPA only 70%. In patients without metastatic disease the sensitivity of combined measurement increased to 62% (19).

The importance of the presence of oestrogen and/or progesterone hormone receptors is obvious, as there is a significant relapse-free interval in the presence of the progesterone receptor. This receptor seems to play a more important role than the oestrogen receptor (20).

There are discussions about the usefulness of several markers like HCG, interferon, serum acute phase proteins, α2-pregnancy-associated glycoprotein, tumor-associated antigen, lipid-bound sialic acid or, for example, hydroxyprolin excretion in breast cancer, but none of these potential markers is well established as yet (21–25).

In conclusion, it has to be stated that CEA values correlate with the stage of disease. They are of limited use for prognosis. Serial determinations are indicated for patient follow-up.

CA 15-3 has a higher sensitivity than CEA and should be measured as well as TPA in the follow-up of breast cancer patients. This increase of sensitivity indicates the combined use of CEA, CA 15-3 and TPA.

OVARIAN CARCINOMA

Ovarian cancer accounts for more annual deaths than cancer of the uterine cervix and corpus together. In early stages it is mostly asymptomatic and undetectable. Indeed, 70% of the patients have metastases outside the pelvis at diagnosis. The natural history also precludes accurate monitoring of disease status. Thus, second look laparatomy is advocated, although this is an invasive procedure with an inherent morbidity. The procedure is not associated with any survival advantage and the inability to exclude residual or distant micrometastases is illustrated by the relapse rate among patients with a complete surgical response (26).

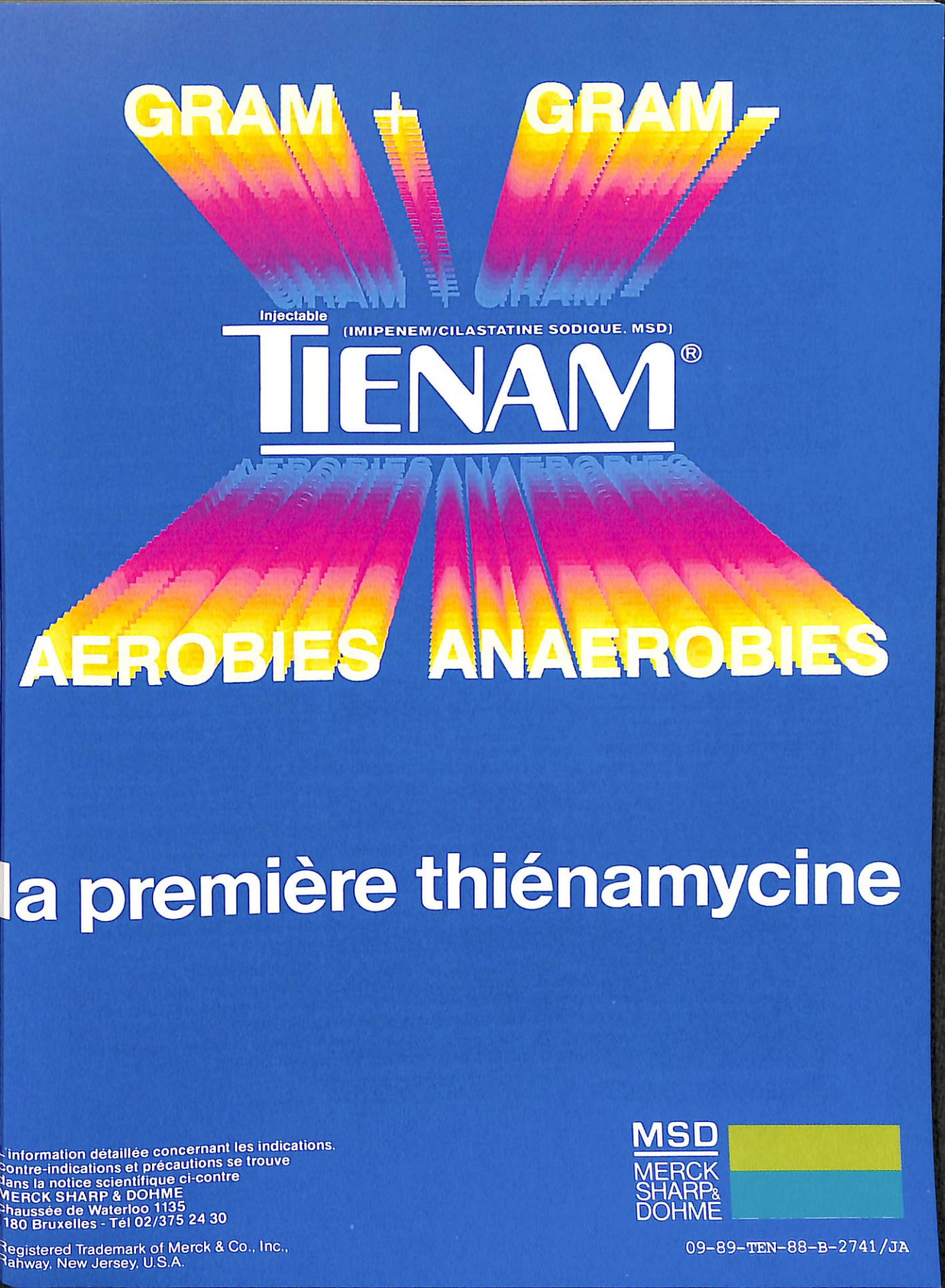
Postoperative chemotherapeutic treatment of ovarian carcinoma is the therapy of choice to reach a complete reduction of the tumor and of residual or distant micrometastases. Therefore, cytostatics are administered for curative reasons. In ovarian cancer response rates in the range of 60–95% can be reached by combination polychemotherapies, while only a small number of patients with advanced disease can be cured (27,28).

The existence of an effective therapy emphasizes the need for sensitive tumor markers as, at second look laparatomy, 30–70% of all patients in complete, clinically diagnosed remission after chemotherpay show persistent disease (28).

The detection of recurrent disease with the indication of further treatment (second look surgery, continuation or change of chemotherapy) has been, besides the standard clinical procedures, facilitated by tumor marker determination in the past.

CA 125

During recent years a large number of antigens have been detected in ovarian cancer. Bast developed a monoclonal immunoglobulin (OC 125) by somatic hybridization of spleen cells from mice immunized with an epithelial


GRAM +
GRAM -
Injectable
(IMIPENEM/CILASTATINE SODIQUE, MSD)
TIENAM®
AEROBIES ANAEROBIES
la première thiénamycine
information détaillée concernant les indications.
contre-indications et précautions se trouve
dans la notice scientifique ci-contre
MERCK SHARP & DOHME
chaussée de Waterloo 1135
180 Bruxelles - Tél 02/375 24 30
MSD
MERCK
SHARP&
DOHME
Registered Trademark of Merck & Co., Inc.,
Rahway, New Jersey, U.S.A.
09-89-TEN-88-B-2741/JA

DENOMINATION

Tienam® 250 Tienam® 500

(imipenem/cilastatine sodique, MSD)

TITULAIRE D'ENREGISTREMENT
MERCK SHARP & DOHME
Chaussée de Waterloo 1135 - 1180 Bruxelles

COMPOSITION
TIENAM® 250: Imipenem monohydrate eq. Imipenem anhydricum 250 mg -Cilastatinum natrium eq. Cilastatinum 250 mg - Natrii hydrogenocarbonas pro tegena una.
TIENAM® 500: Imipenem monohydrate eq. Imipenem anhydricum 500 mg -Cilastatinum natrium eq. Cilastatinum 500 mg - Natrii hydrogenocarbonas pro tegena una.

FORMES, VOIES D'ADMINISTRATION ET CONDITIONNEMENT
TIENAM® 250: poudre pour solution à perfuser par voie intraveineuse, flacon unidose de 50 ml.
TIENAM® 500: poudre pour solution à perfuser par voie intraveineuse, flacon unidose de 120 ml.

PROPRIETES
Le TIENAM® (imipenem/cilastatine sodique, MSD) est un antibiotique à usage parentéral, large-spectre appartenant à la classe des bêtalactamines. Le TIENAM® est fait de deux composants: (1) l'imipenem, premier antibiotique d'une nouvelle classe de bêta-lactamines, les thiénamycines; et (2) la cilastatine sodique, inhibiteur enzymatique spécifique, qui bloque le métabolisme de l'imipenem au niveau des reins et accroît considérablement la concentration de l'imipenem dans le tractus urinaire. L'imipenem et la cilastatine sodique constituent le TIENAM® dans un ratio pondéral de 1:1.
L'imipenem, également appelé N-formimidoyl-thiénamycine, est un dérivé semi-synthétique de la thiénamycine.
Les antibiotiques de la classe des thiénamycines, à laquelle appartient l'imipenem, sont caractérisés par une action bactéricide puissante dont le spectre est plus large que celui de tout autre antibiotique connu. Chimiquement, les thiénamycines se distinguent par des éléments structurels originaux, qui d'une part rendent l'imipenem plus actif à l'égard des protéines de la paroi cellulaire bactérienne, renforçant son action bactéricide et d'autre part lui confèrent une stabilité exceptionnellement grande à l'égard des bêtalactamases bactériennes.

Microbiologie
Le TIENAM® est un inhibiteur puissant de la synthèse de la paroi cellulaire bactérienne et s'avère bactéricide à l'égard d'un large spectre d'agents pathogènes Gram-positifs et Gram-négatifs, aérobies et anaérobies. Le TIENAM® possède un large spectre d'action à l'égard des germes Gram-négatif, mais de plus il possède la caractéristique de conserver, à l'égard des germes Gram-positif, une puissance que ne possédaient jusqu'à présent que les bêtalactamines les plus anciennes à spectre étroit. Cette activité anti-bactérienne équilibrée permet de réduire les risques d'une surinfection due à des espèces bactériennes non-sensibles. Le spectre d'action du TIENAM® comprend Pseudomonas aeruginosa, Serratia sp et Enterobacter, Staphylococcus aureus, Streptococcus faecalis et Bacteroides fragilis, un groupe varié de pathogènes à problèmes, généralement résistants à d'autres antibiotiques.

Liste des germes sensibles (CMI $_{90}$ ≤ 8 mcg/ml)		
CMI $_{90}$ 0,01 - 0,1	CMI $_{90}$ 0,1 - 1	CMI $_{90}$ 1 - 8
Aérobies Gram +		
- Streptococcus sp (gr A, B, C, G)	- Staphylococcus aureus - Listeria monocytogenes	- Staph. aureus méthicilline - R* - Staph. epidermidis - Strept. faecalis** (Gr D ou enterococque) - Nocardia asteroides

* Les valeurs de CMI$_{90}$ pour le Staphylococcus aureus méthicilline-R se situent entre 4 et 8 mcg/ml. Le S. aureus méthicilline-R doit dès lors être considéré comme moins sensible (voir rubrique posologie).
** Certains streptocoques du groupe D ne sont pas sensibles au TIENAM®.

Aérobies Gram -	- E. coli - Klebsiella sp - Acinetobacter sp - Edwardsia comodens - Moraxella sp - Neisseria gonorrhoeae - Neisseria meningitidis - Shigella sp - Yersinia enterocolitica - Citrobacter sp - Salmonella typhi	- Enterobacter sp - Serratia sp - Proteus/providencia sp - P. mirabilis, P. morganii, P rettgeri, P vulgaris* - Pseudomonas aeruginosa** - Alcaligenes - Brucella melitensis - Haemophilus influenzae

* Les valeurs de CMI$_{90}$ pour le P. vulgaris se situent entre 4 et 8 mcg/ml. Le P. vulgaris doit dès lors être considéré comme moins sensible (voir rubrique posologie).
** Le Pseudomonas maltophilia et certaines souches de Pseudomonas cepacia ne sont généralement pas sensibles au TIENAM®.

Anaérobies Gram +		
- Peptococcus sp	- Clostridium perfringens	- Clostridium difficile*
- Peptostreptococcus sp	- Clostridium sp.	- Eubacterium sp

* Les valeurs de CMI$_{90}$ pour le C. difficile se situent entre 4 et 8 mcg/ml. Le C. difficile doit dès lors être considéré comme moins sensible (voir rubrique posologie).

Anaérobies Gram -		
- Campylobacter fetus	- Bacteroides fragilis - Fusobacterium sp - Veillonella sp	

Il n'y a pas de résistance croisée entre l'imipenem et les autres antibiotiques de la classe des bêta-lactamines actuellement disponibles. En raison de sa résistance aux bêta-lactamases, l'imipenem conserve sa pleine activité vis-à-vis de la majorité des souches Gram-négatif et Gram-positif résistantes à un ou plusieurs antibiotiques, y compris les céphalosporines, la carbenicilline et les uréidopenicillines.

PHARMACODYNAMIQUE
Le TIENAM® est un puissant inhibiteur de la synthèse de la paroi bactérienne et est bactéricide à l'égard d'un large spectre de pathogènes, Gram-positif, Gram-négatif, aérobiques et anaérobiques. Le TIENAM® résiste à la dégradation par les bêta-lactamases ce qui le rend actif vis-à-vis d'un pourcentage important de souches résistantes aux autres bêta-lactamines. De plus, c'est un puissant inhibiteur des bêta-lactamases de certaines bactéries Gram-négatif telles que le Pseudomonas aeruginosa, Serratia sp et Enterobacter sp qui sont naturellement résistantes à la plupart des bêta-lactamines.

Imipenem
L'administration intraveineuse de TIENAM® établie sur 20 minutes chez des volontaires sains, engendre des taux plasmatiques maxima d'imipenem, allant de 14 à 24 mcg/ml pour la dose de 250 mg, de 21 à 58 mcg/ml pour la dose de 500 mg, et de 41 à 83 mcg/ml pour la dose de 1000 mg.
Les taux plasmatiques maxima moyens d'imipenem, après administration de doses de 250, de 500 et de 1000 mg, sont respectivement de 20, de 35 et de 65,5 mcg/ml. Avec ces doses, les taux plasmatiques d'imipenem lomment en-deçà de 1 mcg/ml ou moins, en 4 à 6 heures. La demi-vie plasmatique de l'imipenem est d'une heure. Approximativement 70% de l'antibiotique administré sont retrouvés intacts dans les urines endéans les 10 heures, ensuite plus aucune excrétion urinaire de la substance n'est décelable.
Les concentrations urinaires d'imipenem dépassent 10 mcg/ml, parfois 8 heures encore après l'administration d'une dose de 500 mg de TIENAM®. Le reste de la dose administrée se retrouve dans l'urine sous forme de métabolites dépourvus d'activité antibactérienne; l'élimination fécale de l'imipenem est essentiellement nulle.
Aucune accumulation d'imipenem dans le plasma ou dans l'urine n'est observée chez des patients ayant une fonction rénale normale, même après l'administration de TIENAM® à la fréquence de toutes les 6 heures.
L'administration concomitante de TIENAM® et de probénécide provoque une augmentation minime des taux plasmatiques et de la demi-vie plasmatique de l'imipenem. La quantité d'imipenem présente dans les urines est réduite de 70% à environ 00% de la dose, lorsque le TIENAM® est administré en même temps que le probénécide.
La liaison protéique de l'imipenem est d'environ 20% chez l'homme.

Cilastatine
La cilastatine est un inhibiteur spécifique de l'enzyme déhydropeptidase-I; elle inhibe efficacement le métabolisme de l'imipenem, de sorte que l'administration concomitante d'imipenem et de cilastatine permet d'obtenir des taux anti-bactériens thérapeutiques d'imipenem tant dans l'urine que dans le plasma.
Les taux plasmatiques maxima de la cilastatine après une administration intraveineuse de TIENAM® de 20 minutes, sont de 15 à 25 mcg/ml pour la dose de 250 mg, de 31 à 49 mcg/ml pour la dose de 500 mg, et de 58 à 88 mcg/ml pour la dose de 1000 mg. La demi-vie plasmatique de la cilastatine est d'environ 1 heure. Approximativement 70% de la dose de cilastatine apparaissent dans les urines. Environ 10% sont retrouvés sous forme de métabolite N-acétyl, qui exerce à l'égard de la déhydropeptidase une activité inhibitrice comparable à celle de la substance-mère. L'activité de la déhydropeptidase-I dans les reins se normalise peu après l'élimination de la cilastatine du sang circulant.
L'administration concomitante de TIENAM® et de probenecide double les taux plasmatiques ainsi que la demi-vie de la cilastatine, mais n'a aucun effet sur la quantité retrouvée dans les urines.

INDICATIONS
Le TIENAM® est indiqué dans le traitement des formes graves des infections suivantes, lorsqu'elles sont dues à des germes sensibles: - infections intra-abdominales -infections des voies respiratoires inférieures - infections gynécologiques - septicémie - infections du tractus génito-urinaire - infections des os et des articulations -infections de la peau et des tissus mous -endocardite.
Les données concernant l'usage du TIENAM® dans le traitement de la méningite aiguë sont actuellement insuffisantes pour permettre de recommander l'usage du TIENAM® dans cette indication.
Le TIENAM® s'avère généralement aussi efficace en monothérapie dans le traitement d'infections graves, y compris les infections mixtes ou polymicrobiennes, qui exigent classiquement un traitement antibiotique combiné.
Le plupart de ces infections mixtes sont associées à une contamination due à la flore fécale ou à la flore vaginale, cutanée et buccale. Le pathogène aérobique que l'on rencontre le plus couramment dans ces infections mixtes est le Bacteroides fragilis, qui est généralement résistant aux aminoglycosides, aux céphalosporines et aux pénicillines. Le Bacteroides fragilis est cependant habituellement sensible au TIENAM®.
Le TIENAM® est utile en tant que traitement initial des infections dont on ignore l'étiologie, en attendant l'identification des agents responsables.
Le TIENAM® est généralement efficace dans le traitement d'infections provoquées par des micro-organismes dotés d'une résistance naturelle ou acquise à l'égard d'autres antibiotiques; on retrouve traditionnellement parmi les souches à problèmes le Pseudomonas aeruginosa, le Staphylococcus aureus, le Streptococcus faecalis et le Bacteroides fragilis.

POSOLOGIE ET MODE D'EMPLOI
La posologie du TIENAM® doit être déterminée en fonction de la gravité de l'infection, de la sensibilité à l'antibiotique du (des) micro-organisme(s) responsable(s), et de l'état du patient.
Etant donné le profil de son activité, le TIENAM® est particulièrement indiqué pour le traitement des infections graves.

Posologie chez l'adulte
Dans les infections sévères, la dose quotidienne, (exprimée en mg d'imipenem) est de 500 mg toutes les 6 heures. Dans les infections très graves, la dose quotidienne sera de 1000 mg toutes les 8 heures. Dans les infections à risque vital ou dans les infections dues à des micro-organismes moins sensibles, la dose quotidienne de TIENAM® pourra être augmentée jusqu'à la posologie quotidienne maximale qui est de 1000 mg toutes les 6 heures. La posologie quotidienne maximale est de 50 mg/kg/jours sans dépasser 4 g par jour.
Chaque dose de 250 mg ou de 500 mg doit être administrée en perfusion intraveineuse durant 20 à 30 minutes. Les doses de 1000 mg doivent être perfusées en 40 à 60 minutes. La vitesse de perfusion peut être ralentie chez les patients qui présentent des nausées durant l'administration. (Pour les autres informations pratiques voir la rubrique 'Précautions particulières')

Posologie chez l'enfant
Chez l'enfant et le nourrisson âgé de plus de 3 mois la dose quotidienne totale recommandée est de 60 à 100 mg/kg à diviser en 4 doses égales administrées toutes les 6 heures. Les posologies les plus élevées seront utilisées chez les nourrissons et les jeunes enfants. La dose totale ne pourra excéder 2 g. Les données actuellement disponibles sont insuffisantes que pour permettre de recommander une posologie optimale en cas d'insuffisance rénale chez l'enfant et le nourrisson.
L'efficacité et la tolérance du TIENAM® chez le nourrisson de moins de 3 mois n'ont pas encore été établie. Dès lors l'usage du TIENAM® n'est pas recommandé chez les enfants qui ont de la tranche d'âge 0 à 3 mois.

Posologie dans l'insuffisance rénale chez l'adulte
Comme pour les patients ayant une fonction rénale normale, la posologie sera basée sur la sévérité de l'infection. La posologie maximale en fonction du degré d'insuffisance du patient est indiquée dans le tableau 1. La posologie indiquée est basée sur un poids corporel de 70 kg. La dose administrée sera réduite de façon proportionnelle pour les patients ayant un poids inférieur.

TABLEAU 1

POSOLOGIE MAXIMALE EN FONCTION DU DEGRE D'INSUFFISANCE RENALE

Fonction rénale (clairance de la créatinine en ml/min/1,72 m²)	Dose (g)	Intervalle entre les doses (heures)	Posologie quotidienne maximale (g)
insuffisance légère 31 - 70	0,5	6 - 8	1,5 - 2
Insuffisance modérée 21 - 30	0,5	8 - 12	1 - 1,5
Insuffisance grave* 0 - 20	0,25 - 0,5	12	0,5 - 1,0

* Les patients ayant une clairance de la créatinine < 5 ml/min devraient être dialysés.

Le TIENAM® est éliminé par hémodialyse. Une dose supplémentaire équivalente à la dose d'entretien sera administrée après la dialyse à moins que l'administration de la dose suivante ne soit prévue endéans les 4 heures qui suivent la dialyse.
L'état de la fonction rénale chez le patient âgé peut ne pas être évalué de manière adéquate si l'on se base uniquement sur l'urée et la créatinine plasmatique. L'évaluation de la clairance de créatinine est fortement conseillée pour établir la posologie chez ces patients.

CONTRE-INDICATIONS
Le TIENAM® est contre-indiqué chez les patients qui ont manifesté une hypersensibilité à l'un ou l'autre des composants du produit

EFFETS SECONDAIRES
Le TIENAM® est généralement bien toléré. Les effets secondaires exigent rarement l'interruption du traitement, ils sont généralement bénins et transitoires, les effets secondaires graves sont rares. Les effets secondaires les plus courants sont des réactions locales consécutives à l'injection intraveineuse

Réactions locales
Erythème, douleur et induration locales, thrombophlébite

Réactions allergiques
Eruption, prurit, urticaire, fièvre, réactions anaphylactiques
Les données actuellement disponibles ne permettent pas d'établir une corrélation positive ou négative en ce qui concerne l'existence éventuelle d'une allergie croisée entre le TIENAM® et les pénicillines ou les céphalosporines.

Réactions digestives
Nausées, vomissements, diarrhée, colite pseudomembraneuse

Sang
Eosinophilie, leucopénie, neutropénie, thrombocytopénie et thrombocytose, diminution de l'hémoglobine ont été rapportées. Le test de Coombs direct peut devenir positif chez certaines personnes

Fonction hépatique
Une augmentation légère des transaminases sériques, de la bilirubine et/ou des phosphatases alcalines sériques a été signalée

Fonction rénale
Une élévation de la créatinine sérique et de l'urée sanguine a été observée. On a pu observer une coloration rouge des urines chez les patients appartenant à la tranche d'âge pédiatrique. Ce phénomène n'a aucune signification pathologique et ne doit pas être confondu avec une hématurie

Système nerveux central
De même que pour d'autres antibiotiques de type bêta-lactamine, des réactions indésirables au niveau du système nerveux central ont été signalées, telles qu'une activité myoclonique, des états confusionnels, des convulsions épileptiformes. Ces réactions ont surtout été constatées chez des patients atteints de troubles du système nerveux central (par ex., lésions cérébrales ou anamnèse récente de crises convulsives) présentant une altération de la fonction rénale et dès lors susceptibles de présenter une accumulation du produit.

Effets indésirables complémentaires
Pour les effets indésirables suivants il n'a pas été établi de relation de cause à effet: Système gastro-intestinal: colite hémorragique, gastro-entérite, douleurs abdominales, glossite, hypertrophie des papilles linguales, pyrosis, douleur pharyngée, salivation excessive

SNC: vertige, somnolence, encéphalopathie, paresthésies, céphalées

Organes des sens: perte transitoire de l'ouïe chez des patients souffrant déjà de perturbations du sens de l'ouïe, bourdonnements d'oreilles

Système respiratoire: gêne thoracique, dyspnée, hyperventilation, douleur thoracique transfixiante

Système cardiovasculaire: hypotension, palpitations, tachycardie

Système génito-urinaire: oligurie/anurie, polyurie

Peau: érythème, oedème facial, rougeur, cyanose, hyperhidrose, modifications de la texture cutanée, candidose, prurit vulvaire

Réactions générales: polyarthralgies, asthénie/faiblesse

PRECAUTIONS
On a rapporté des cas de colite pseudomembraneuse avec le TIENAM®. La gravité de la colite peut aller de l'affection bénigne à la pathologie potentiellement mortelle. C'est pourquoi il convient d'être prudent en prescrivant des antibiotiques aux individus dont les antécédents comprennent des affections gastro-intestinales, et particulièrement une colite. Il importe d'envisager la possibilité d'une colite pseudomembraneuse lorsqu'un patient développe une diarrhée dans le cadre d'un traitement antibiotique. Bien que, selon certaines études, une toxine produite par le Clostridium difficile soit une des causes majeures de la colite associée aux antibiotiques, d'autres causes doivent également être prises en considération. Le traitement classique de la colite pseudomembraneuse consiste en l'administration per os de vancomycine. Etant donné que l'on ignore actuellement s'il existe une allergie croisée entre le TIENAM® et les pénicillines ou les céphalosporines, les patients présentant une allergie connue à ces antibiotiques seront traités avec prudence

Système nerveux central
Tout comme avec les autres bêta-lactamines, on a rapporté des effets indésirables avec le TIENAM® au niveau du système nerveux central, tels que activité myoclonique, états de confusion ou convulsions. Ces effets indésirables se sont produits le plus souvent chez des patients présentant une pathologie au niveau du SNC (par ex. lésions cérébrales ou antécédents de convulsions) et présentant une altération de la fonction rénale et dès lors susceptibles de présenter une accumulation du produit. Par conséquent il est particulièrement indispensable chez ces patients de respecter la posologie recommandée (voir section posologie).
Il faut maintenir un traitement anticonvulsif chez les patients ayant une pathologie de type convulsif connue. Les patients présentant des tremblements localisés, des secousses myocloniques ou des convulsions reçoivent un traitement antiépileptique. Si les symptômes persistent, on diminuera les doses de TIENAM® ou on arrêtera le traitement.

Précautions particulières
TIENAM® est tamponné avec du bicarbonate de sodium de sorte que le pH de la solution se situe entre 6,5 et 7,5. Il n'y a pas de modification significative de ce pH si les solutions sont préparées et utilisées en suivant les recommandations ci-dessous.
TIENAM® 250 contient 10,8 mg de sodium (0,8 mEq.) et TIENAM® 500 contient 37,7 mg de sodium (1,6 mEq.).
Le contenu de TIENAM® sera dilué suivant les indications du tableau 2. La poudre se dissous endéans les 3 minutes d'agitation constante par mouvements du poignet, ou par agitation vigoureuse intermittente. On obtient une solution claire, incolore à jaune. Toute variation de couleur à l'intérieur de ces limites n'influence pas l'efficacité du produit.

TABLEAU 2: Reconstitution du TIENAM®

Dose de TIENAM® (mg d'imipenem)	Volume de diluant à ajouter (ml)	Concentration moyenne approximative de TIENAM® (mg/ml d'imipenem)
250	50	5
500	100	5

Solutions compatibles
Serum physiologique, solution de glucosé 5 ou 10% dans l'eau, glucose 5% dans une solution physiologique, glucose 5% additionné de 0,02% de NaHCO3 (238 mM %) ou de 0,15 de KCl (2 mEq%) ou dans une solution de mannitol 2,5 , 5 ou 10%.
Attention: Le TIENAM® est chimiquement incompatible avec des solutions qui contiennent du lactate.
Le TIENAM® en solution ne sera ni mélangé ni ajouté à d'autres solutions contenant des antibiotiques.

Stabilité avant la reconstitution
La poudre sèche doit être conservée à température ambiante (15-25°C)

Stabilité en solution
Le TIENAM® en solution reste stable pendant 4 heures à température ambiante ou 24 heures au réfrigérateur lorsqu'il est reconstitué à l'aide des solvants cités ci-dessus.
Chaque dose de 250 mg ou de 500 mg doit être administrée en perfusion intraveineuse durant 20 à 30 minutes. Les doses de 1000 mg doivent être perfusées en 40 à 60 minutes. La vitesse de perfusion peut être ralentie chez les patients qui présentent des nausées durant l'administration

GROSSESSE ET LACTATION
Grossesse. L'utilisation du TIENAM® n'a pas été étudiée chez la femme enceinte; dès lors le TIENAM® ne sera prescrit au cours de la grossesse qu'en cas de force majeure
Lactation. On ignore si le TIENAM® est excrété dans le lait maternel. Si l'utilisation du TIENAM® est jugée indispensable, l'allaitement sera interrompu

INTERACTIONS
Les données actuellement disponibles ne font présager aucune interaction médicamenteuse indésirable (voir néanmoins le paragraphe Solutions compatibles dans la section Précautions particulières)

SURDOSAGE
Il n'existe pas de données concernant le surdosage (Le TIENAM® est hémodialysable)

CONSERVATION
1. Voir rubrique Stabilité dans le paragraphe Précautions particulières
2. Stabilité: voir emballage Ex.: signifie expiration et est suivi de 2 groupes de chiffres, le premier indiquant le mois à partir duquel le médicament est considéré comme périmé (et ce, dès le 1er jour de ce mois), le 2ème groupe de chiffres indiquant l'année.

DELIVRANCE
Le TIENAM® est uniquement disponible pour l'usage hospitalier

DERNIERE MISE A JOUR DE LA NOTICE SCIENTIFIQUE: 13/10/86

MSD
MERCK SHARP & DOHME

® = Marque déposée

ovarian carcinoma cell line. The murine monoclonal antibody OC 125 reacts with the antigen CA 125 which is expressed by more than 80% of non-mucinous epithelial ovarian cancers (29). Also, a radioimmunoassay has been developed to detect CA 125 in serum as a marker for ovarian carcinoma (30).

The sensitivity, the percentage of correlation of positive CA 125 values and clinically evident disease, investigated in nine recent studies in more than 700 patients is given in Table 4 (26,28,31–36).

The cut-off level of CA 125 serum measurement was determined by most investigators with 35 U/ml, but using serial determinations it is possible to detect a tumor progression in the range of even 15–35 U/ml (28).

(over 35 U/ml) are measurable, even up to 96% (35). A difference in the sensitivity of epithelial tumors can be shown comparing patients of all stages with Fish's and Cruickshank's preoperative investigations (26,36,40,41).

The number of patients in the histological groups other than those with serous carcinomas is too small to draw meaningful conclusions from these determinations of CA 125.

With regard to the degree of differentiation, patients with grade 2 and 3 tumors showed higher levels than borderline and grade 1 tumors (36). The positive CA 125 levels correlate with the tumor burden as only 63% of patients with a tumor burden in excess of 2 cm

TABLE 4. Sensitivity of the marker CA 125 in ovarian carcinoma

			Cut-off	No. of patients
Bast	1983	82%	35 U ml^{-1}	101
Ricolleau	1984	92%	35 U ml^{-1}	38
Canney	1984	83%	35 U ml^{-1}	58
Krebs	1986	96%	25 U ml^{-1}	45
Lahousen	1986	94%	35 U ml^{-1}	80
Kivinen	1986	91%	35 U ml^{-1}	112
Cruickshank	1987	73%	35 U ml^{-1}	52
Vergote	1987	86%	35 U ml^{-1}	227

The specificity of CA 125 for ovarian carcinoma has to be judged poor, as the marker is also associated with other malignancies. Therefore this marker is not useful for differential diagnosis of carcinomas of unknown origin (36).

In a number of benign lesions, such as pelvic inflammatory disease, endometriosis and especially in liver cirrhosis, as well as in pregnancy, elevated CA 125 levels are shown (31,32,37).

With regard to histology, CA 125 is frequently associated with epithelial ovarian cancer (31,38). The marker is elevated in up to 92% of patients with epithelial tumors. In the most frequent group of ovarian tumors, the serous adenocarcinomas, enlarged levels show elevated marker levels, compared to 76% with a bulk between 2 and 10 cm. The levels of nearly 100% of all patients are elevated if the bulk exceeds 10 cm (Table 6).

Low levels of CA 125 are associated with early clinical stages (small tumor burden), predicting a response to chemotherapy and usually showing low recurrence rates. High preoperative marker values indicate advanced disease with poor response to chemotherapy (33).

Serial measurements of CA 125 during chemotherapy correlate with the clinical course of disease (Table 7). It can be shown by this table that an increasing CA 125 level is always associated with disease progression.

TABLE 5. Epithelial ovarian carcinomas and elevated CA 125 levels

Histology	Vergote (36)	Dhokia (41)	Fish (40)	Cruickshank (26)
	Overall		Pre-operative	
	Number of patients/number with elevated CA 125			
Serous	68/61	37/31	43/25	13/9
Mucinous	4/3	5/4	7/2	9/5
Endometroid	8/6	12/7	9/3	2/2
Clear cell	6/3	5/5	2/2	4/2
Mixed	10/9	—	3/1	—
Undifferentiated	4/3	26/24	22/16	13/12
Unclassifiable	12/11	—	—	—
Total	112/96 (86%)	85/71 (84%)	86/49 (57%)	41/30 (73%)

TABLE 6. Percentage of positive CA 125 levels in correlation to tumor burden in ovarian carcinoma

Tumor bulk		No. of patients
< 2 cm	63%	16
2–20 cm	76%	17
> 10 cm	100%	24

Canny (1984); cut-off: 35 U/ml

Unchanged marker levels do not indicate a response to treatment in any case, while decreasing levels are associated with response to treatment (31,33,34,36). In approximately 92% of patients with ovarian cancer CA 125 estimations are able to monitor response to therapy or progression (32–34,36).

The predictive value of CA 125 was evaluated by Khoo, with second look surgery. In his study, he found the presence of tumors in 92% of carcinoma patients with raising or persistently high levels, while declining or negative values predict the absence of tumor in only 50% of patients. This might indicate that CA 125 lacks sensitivity in detecting small tumor masses (39). However, a normal CA 125 level does not exclude the presence of disease (36). An acute elevation of CA 125 in the first week following chemotherapy predicts a good response to treatment (30,40).

A new method using a panel of the monoclonal antibodies HMFG1 and HMFG2 in combination with CA 125, seems to lead to an increase in sensitivity of 95% without loss of specificity (41). The assay of CA 125 seems to be a reliable non-invasive method for monitoring ovarian cancer patients.

CEA

The value of plasma CEA determination in ovarian carcinoma is limited, as the sensitivity is low and the rate of false negative values is high. Serial determinations might be helpful, predicting relapse only in patients with mucinous tumors (42,43).

OTHER MARKERS

In several studies, cancer antigens, CA 19-9 and CA 50, dehydroepiandosterone sulfate, galactosyltransferase, tissue polypeptide antigen and ferritin have been investigated. There are some indications to use these markers for ovarian cancer, but further studies are necessary to define their benefit (28,32,44–47).

Spona found in a study for adjuvant chemotherapy in ovarian cancer, measuring the oestrogen and progesterone receptors, that receptor assays may provide a prognostic index. The survival rate of patients with ovarian carcinoma is greater in patients with both receptors positive than in those who lack receptors. The prognostic importance seems

TABLE 7. Correlation of disease status and CA 125 levels in ovarian carcinoma in response to chemotherapy (no. of patients)

CA 125 levels	Clinical status			
	Response	Static	Progression	
Decreasing	20	1	0	Bast (31)
	12	3	0	Canney (33)
	21	0	0	Krebs (34)
	44	3	2	Vergote (36)
No change	0	5	2	Bast (31)
	0	1	1	Canney (33)
	0	2	2	Krebs (34)
	0	13	3	Vergote (36)
Increasing	0	0	17	Bast (31)
	0	0	16	Canney (33)
	0	0	18	Krebs (34)
	0	0	36	Vergote (36)

to be equal for ovarian and breast cancer patients concerning survival and risk of recurrence (48).

CERVICAL AND ENDOMETRIAL CANCER

In the management of the most common malignant diseases of the uterus, no tumor marker is established monitoring these diseases. Only little value indicates β-2 microglobulin measurement in these tumors (49).

GESTATIONAL TROPHOBLASTIC DISEASE (GTN)

GTN is a rare tumor of the placenta with an incidence from 1 in 600 to 1 in 1200 pregnancies. The characteristics of GTN, on the one hand its occurrence in young women and the propensity for early metastasis, on the other hand its rapid response to chemotherapy combined with an excellent monitoring, makes it interesting for marker investigations (50).

Laurin's results of chemotherapeutic treatment and adjuvant surgery of choriocarcinoma and invasive mole in 359 patients are given in Table 8. For nonmetastatic disease cure rates of 100% and for disseminated tumors cure rates of 83% are shown in Table 8 (51).

TABLE 8. Treatment results of choriocarcinoma and invasive mole

Diagnosis	No. of patients	Cure rates (%)
Choriocarcinoma	159	129 (81)
Metastatic	105	75 (71)
Nonmetastatic	54	54 (100)
Invasive mole	200	200 (100)
Metastatic	69	69
Nonmetastatic	131	131
Total	359	329 (92)
Metastatic	174	144 (83)
Nonmetastatic	185	185 (100)

Source: Laurin (1982), modified.

HCG is elevated in all trophoblastic tumors, and reaches almost 100% sensitivity and specificity (52,53).

The glycoprotein HCG consists of the α- and β-chain. The α-chain is also found in hypophyseal glycoproteins like the human luteinizing hormone. The β-chain is measurable by a radioimmunoassay specific for HCG. Healthy and non-pregnant women have a serum β-HCG value below 1 ng/ml (equivalent to 5 mIU/ml) (54).

The β-HCG levels are used to define response to chemotherapy and a stop of chemotherapy is indicated when a zero HCG titer remains during measurements for 3 weeks (55). Treatment has to be continued for several cycles after the first normal marker value, as an enlarged tumor burden of more than 10^4 trophoblastic cells is able to produce measurable β-HCG levels. The aim of the chemotherapy is the complete destruction of all malignant cells (56). Relapses are first detected by a rise in the HCG titer (51).

Poor prognosis has to be expected in patients with a serum β-HCG value greater than 42 000 mIU/ml or an urinary value in excess of 100 000 IU/l. (50).

The excellent monitoring and effective chemotherapeutic treatments available for this disease correlates with overall cure rates of about 90%. This indicates the surgical removal of resistant tumor masses only for cases with resistance to cytostatic treatment or complications like extensive haemorrhage (57).

It is therefore possible to avoid surgery, if the marker values go down in parallel with the effective chemotherapy. This is important for young women who still want to have children after treatment.

REFERENCES

1. BONADONA G., VALAGUSSA P., ROSSI A., TANGINI G., BAJETTA E., MARCHINI S. and VERONESI U.: CMF adjuvant chemotherapy in operable breast cancer, in JONES S. E. and SALOMON S. E. (eds): Adjuvant Therapy of Cancer II, p. 227. New York, Grune and Stratton, 1979.
2. GÜNCZLER P., OGRIS E., DANMAYER E., DENCK H. and ALTH G.: Vergleichende Evaluation der Tumormarker CA 15-3 und CEA beim Mammakarzinom. Referat beim 1. Alp Workshop für Senology, Oberlech, 1987.
3. HOFFMANN L.: Die Bedeutung neuer Tumormarker für das Mammakarzinom und das Ovarialkarzinom. Dt. med. Wschr 112, 874, 1987.
4. HORN Y., HACOHEN D., ZEIDMAN J., WALACH N., SHARF S., HELLER A. and SALZBERG S.: Carcinoembryonic antigen and interferon as tumor markers in breast cancer. J. surg. Oncol. 22, 254, 1983.
5. HEIM M., SAUER B., SCHNITZLER G., HAUX P. and FELDMANN U.: Bedeutung des Carcinoembryonalen Antigens für die Therapiekontrolle von fortgeschrittenen Mammakarzinomen. Tum. diag. Therap. 5, 220, 1984.
6. SCHATZ C., LIEVEN H., MULDERS M., ROWOLD J., STRACKE H., MÜLLER H., GREBE S. F. and SCHATZ H.: Die Tumormarker CEA, TPA und CA 19-9 sowie Ferritin und Osteocalcin in der Verlaufskontrole bei Mammakarzinom. Wien klin. Wschr. 23, 873, 1985.
7. MYERS R., SUTHERLAND D., MEAKIN J., KELLEN J., MALKIN D. and MALKIN A.: Carcinoembryonic antigen in breast cancer. Cancer 42, 1520, 1978.
8. FALKSON H., FALKSON G., PORTUGAL M. A., WATT J. and SCHOEMAN S.: Carcinoembryonic antigen as a marker in patients with breast cancer receiving postsurgical adjuvant chemotherapy. Cancer 49, 1859, 1982.
9. BATES S. E. and LONGO D. L.: Tumor markers: value and limitations in the management of cancer patients. Cancer Treat. Rev. 12, 163, 1985.
10. CHATAL J. F., CHUPIN F., RICOLLEAU G., TELLIER J. L., LE MEVEL A., FUMOLEAU P., GODIN O. and LE MEVEL B. P.: Use of serial CEA assays in detection relapses in breast cancer involving high risk of metastases. Eur. J. Cancer 17, 233, 1981.
11. TORMEY D. C., WAALKES T., SNYDER J. J. and SIMON M.: Clinical correlations with carcinoembryonic antigen. Cancer 39, 2397, 1977.
12. VERONESI A., TALAMINI R., LONGHI S., CRIVELLARI D., GALLIGIONI E., TIRELLI U., TROVÒ M. G., MAGRI D., FRUSTACI S., FIGOLI F., ZAGONEL V., TUMOLO S. and GRIGOLETTO E.: CEA in the follow-

Venoruton® forte

Venoruton
le seul venotrope admis au Royaume-Uni
le seul venotrope documenté par plus de 900 études et travaux

Boîtes de 30 et 60 comprimés

PAR JOUR

Solution 10 % GEL

Venoruton® le seul

Composition O-(ß-hydroxyethyl)-rutosides 500 mg, Excip. q.s. ad compr. - Venoruton forte exerce son effet sur la paroi des capillaires dont il augmente la résistance et normalise la perméabilité. Ces propriétés ont été démontrées par différents modèles expérimentaux et chez de nombreux patients souffrant d'insuffisance veineuse chronique, de troubles consécutifs à la radiothérapie ou d'altération vasculaires rétiniennes. Venoruton forte a montré également un effet inhibiteur de l'agrégation des thrombocytes et des érythrocytes de même qu'un effet protecteur sur l'endothélium vasculaire. Venoruton forte représente un traitement judicieux de l'insuffisance veineuse chronique par son effet sur la réduction de l'œdème et celle des autres symptômes, tels que douleurs, crampes, troubles trophiques, dermites variqueuses et ulcères variqueux. Venoruton forte permet d'atténuer les réactions secondaires consécutives à la radiothérapie, telles que cystites, entéroproctites, dysphagies, érythèmes cutanés, etc., réactions qui nécessitent souvent une interruption du traitement. Venoruton forte, par ses effets sur la résistance et la perméabilité des capillaires, permet également de ralentir l'évolution des rétinopathies diabétiques. D'autre part, ses effets sur les caractéristiques rhéologiques du sang permettent d'atténuer les épisodes microthrombotiques et les autres formes d'ischémie vasculaire rétinienne - **Indications** : Douleurs et œdèmes des varices constituées. Varices et hémorroïdes gravidiques. Œdèmes et autres symptômes de l'insuffisance veineuse chronique, syndrome postphlébitique, thrombophlébites superficielles, troubles trophiques, ulcères variqueux et dermites variqueuses. Prévention et traitement des réactions vasculaires et des muqueuses consécutives à la radiothérapie. Adjuvants dans le traitement des rétinopathies associées au diabète, à l'hypertension et à l'artériosclérose et prévention des épisodes d'amaurose fugace - **Contre-indications** : Aucune connue à ce jour. Venoruton forte est bien toléré et permet la prescription d'un traitement prolongé.

Laboratoires Zyma S.A.

Für jeden Fall die richtige Form:

Rheumon® Gel und Creme zur Behandlung rheumatischer Erkrankungen.

Rheuma: Rheumon®

bei normaler Haut
Kühleffekt
Iontophorese
preisgünstige Langzeittherapie

bei trockener Haut
Massageeffekt
unter Verbänden anwendbar
nicht fettend

Traumon® Gel zur Behandlung stumpfer Traumen (Prellungen, Zerrungen, Verstauchungen).

Trauma: Traumon®

Rheuma-Forschung

Sport, Haushalt, Beruf
Kühleffekt
konzentrierte Tiefenwirkung
olympiagetestet

Das umfassende Lokalprogramm.

Zusammensetzung: 1 g Rheumon Gel enthält 50 mg Etofenamat, 1 g Rheumon Creme enthält 100 mg Etofenamat. **Indikationen:** Weichteilrheumatismus, Periarthropathia humeroscapularis, Lumbago, Ischialgie, Tendovaginitis, Bursitis, stumpfe Traumen und Sportverletzungen, Weichteilaffektionen bei Arthrosen und Spondylosen. **Kontraindikationen:** Überempfindlichkeit gegen Etofenamat und Flufenaminsäure. Schwangerschaft, Stillende, Säuglinge und Kleinkinder. **Nebenwirkungen:** Selten Hautreizungen, die sich nach Absetzen rasch zurückbilden. **Hinweis:** Rheumon Gel nicht auf verletzter oder ekzematös veränderter Haut anwenden. **Handelsformen:** Rheumon Gel 40 g; Rheumon Gel 100 g. Rheumon Creme 40 g; Rheumon Creme 100 g; Rheumon Creme 200 g.

Für Luxembourg: Integral S.A., 5, Rue Christophe-Plantin, Tél. 48.56.56

Zusammensetzung: 1 g Traumon Gel enthält 100 mg Etofenamat. **Indikationen:** Sportverletzungen wie Prellungen, Verstauchungen, Zerrungen, Weichteilrheumatismus, Periarthropathia humeroscapularis, Lumbago, Ischialgie, Tendovaginitis, Bursitis, Weichteilaffektionen bei Arthrosen und Spondylosen. **Kontraindikationen:** Überempfindlichkeit gegen Etofenamat, Flufenaminsäure und Propylenglykol. Schwangerschaft, Stillende, Säuglinge und Kleinkinder. **Nebenwirkungen:** Selten Hautrötungen, die sich nach Absetzen rasch zurückbilden. **Besonderer Hinweis:** Traumon Gel soll nicht auf verletzter oder ekzematös veränderter Haut angewendet werden. **Handelsformen:** Traumon Gel 40 g; Traumon Gel 100 g.

TROPON ARZNEIMITTEL KÖLN

up of disease-free breast cancer patients. Tumori 68, 477, 1982.

13. LAMERZ R., LEONHADT H., EHRHART H. and LIEVEN H.: Serial CEA determination in the management of metastatic breast cancer. Oncodevel. biol. Med. I, 123, 1980.
14. COOMBES R. C., POWLES T. J., MITCHELL P., PATEL S. and NEVILLE A.: The value of sequential marker determination following mastectomy. Second Breast Cancer Working Conference, Copenhagen, 1979, p. 12.
15. HAAGENSEN D., KISTER S., VANDEVOORDE J., GATES J., SMART E., HANSEN H. and WELLS S.: Evaluation of CEA as a plasma monitor for human breast carcinoma. Cancer 42, 1512, 1978.
16. HAYES V. and ZURAWSKI D.: Comparison of circulating breast cancer associated antigen CA 15-3 with CEA in patients with breast cancer. Proc. ASCO 5, 12, 1986.
17. STEGER G., MADER R., DITTRICH C., SCHLAPACK O., JAKESZ R., KOLB R. and MOSER K.: Tumormarker und ein neu entwickelter Tumormarkerscore. Wien klin. Wschr. 14, 511, 1987.
18. LÜTHGEN M. and SCHLEGEL G.: CEA und TPA in der klinischen Tumordiagnostik, insbesondere des Mammakarzinoms. Tumordiagnostik 2, 63, 1980.
19. HÜNERMANN B., OEHR P., BIERSACK H. J. and WINKLER C.: Verteilung, Sensitivitat, und Spezifitat von CEA, TPA und CEA × TPA-Marker-Produktwertbildung bei Patientinnen mit Mammakarzinom. Nucl. Compact 14, 4, 1983.
20. ZIELINSKI C. C., KUZMITS R., KUBISTA E., SALZER H., STAFFEN A., AIGINGER P. and SPONA J.: Die Bedeutung der Hormonreceptoren von Mammakarzinomzellen für die Dauer des erkrankungsfreien Intervalls. Wien klin. Wschr. 11, 493, 1985.
21. SULITZEANU D.: Markers in breast cancer. Israel J. med. Sci. 17, 865, 1981.
22. THOMPSON D. K., HADDOW J. E., SMITH D. E. and RITCHIE R. F.: Elevated serum acute phase proteins levels as predictors of disseminated breast cancer. Cancer 51, 2100, 1983.
23. ROWSE A. D., MORRISON M. J., SCOTT P. H., BANKS A. J. and ROGINSKI C.: Hydroxyprolin excretion in the detection of occult metastases from breast cancer. Oncology 39, 287, 1982.
24. DNISTRIAN A. M., SCHWARTZ M. K., KATOPODIS N., FRACCHIA A. A. and STOCK C. C.: Serum lipid bound sialic acid as a marker in breast cancer. Cancer 50, 1815, 1982.
25. ANDERSON J. M., STIMSON W. H., GETTINBY G., JHUNJHUNWALA K. and BURT R. W.: Detection of mammary micrometastases by pregnancy associated α2-glycoprotein and carcinoembryonic antigen. Eur. J. Cancer 15, 709, 1980.
26. CRUICKSHANK D. J., FUELLERTON W. T. and KLOPPER A.: The clinical significance of pre-operative serum CA 125 in ovarian cancer. Br. J. Obstet. Gynaec. 94, 692, 1987.
27. VOGAL S. E., BERENZWEIG M. and KAPLAN B. H.: The CHAD and HAD regimens in advanced ovarian cancer: combination chemotherapy including cyclophosphamide, hexamethylmelamine, adriamycin and *cis*-dichlorodiammineplatinum. Cancer Treat. Rep. 63, 311, 1979.
28. KIVINEN S., KUOPPALA T., LEPPILAMPI M., VUORI J. and KAUPPILA A.: Tumor-associated antigen CA 125 before and during the treatment of ovarian carcinoma. Obstet. Gynec. 67, 468, 1986.
29. BAST R. C. Jr., FEENEY M., LAZARUS H., NADLER L. M., COLWIN R. B. and KNAPP R. C.: Reactivity of a monoclonal antibody with human ovarian carcinoma. J. clin. Invest. 68, 1331, 1981.
30. KLUG T. L., BAST R. C., NILOFF J. M., KNAPP R. C. and ZURAWSKI V. R.: Monoclonal antibody immunradiometric assay for an antigenic determinant (CA 125)

associated with human epithelial ovarian carcinomas. Cancer Res. 44, 1048, 1984.

31. BAST R. C., KLUG T. L., JENISON E., NILOFF J. M. and LACARUS H.: A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. New Engl. J. Med. 15, 883, 1983.
32. RICOLLEAU G., CHATAL J. F., FUMOLEAU P., KREMER M., DOUILLARD J. Y. and CURTET C.: Radioimmunoassay of the CA 125 antigen in ovarian carcinomas: advantages compared with CA 19-9 and CEA. Tumor Biol. 5, 151, 1984.
33. CANNEY P. A., MOOR M., WILKINSON P. M. and JAMES R. D.: Ovarian cancer antigen CA 125: a prospective clinical assessment of its role as a tumor marker. Br. J. Cancer 50, 765, 1984.
34. KREBS H. B., GOPLERUD D. R., KILPATRICK J., MAYERS M. and HUNT A.: Role of CA 125 as tumor marker in ovarian carcinoma. Obstet. Gynec. 67, 473, 1986.
35. LAHOUSEN M.: Der prädikative Wert einer Tumormarker-Kombination für das Monitoing beim Ovarialkarzinom. Wien klin. Wschr. 10, 319, 1986.
36. VERGOTE I. B., BORMER O. P. and ABELER V. M.: Evaluation of serum CA 125 levels in the monitoring of ovarian cancer. Am. J. Obstet. Gynec. 157, 88, 1987.
37. HALILA H., STENMAN U. and SEPPÄLÄ M.: Ovarian cancer antigen in CA 125 levels in pelvic inflammatory disease and pregnancy. Cancer 57, 1327, 1986.
38. BAST R. C. Jr., KLUG T. L. and SCHAETZL E.: Monitoring human ovarian carcinoma with a combination of CA 125, CA 19-9 and CEA. Am. J. Obstet. Gynec. 149, 553, 1984.
39. KHOO S. K., HURST R., WEBB M. and KEARSLEY J. H.: Predictive value of serial CA 125 antigen levels in ovarian cancer evaluated by second look laparotomy. Eur. J. clin. Oncol. 23, 765, 1987.
40. FISH R. G., SHELLEY M. D., MAUGHAN T., ROCKER I. and ADAMS M.: The clinical value of serum CA 125 levels in ovarian cancer patients receiving platinum therapy. Eur. J. Cancer. clin. Oncol. 23, 841, 1987.
41. DHOKIA B., CANNEY P. A., PECTASIDES D., MUNRO A. J., MOOR M., WILKINSON P. M., SELF C. and EPENETOS A. A.: A new immunoassay using monoclonal antibodies HMFG1 and HMFG2 together with an existing marker CA 125 for the serological detection and management of epithelial ovarian cancer. Br. J. Cancer 54, 891, 1986.
42. MARCHAND A., FENOGLIO C. M., PASCAL R., RICHART R. M. and BENNETT S.: Carcinoembrionic antigen in human ovarian neoplasma. Cancer Res. 35, 3807, 1975.
43. LENEHAN P. M., DEMBO A. L., MICELI P. N., MALKIN D. G. and MALKIN A.: Clinical correlations of carcinoembrionic antigen in postoperative patients with epithelial ovarian cancer. Tumor Biol. 7, 389, 1986.
44. SZMENDERA J. J.: Clinical usefullness of three monoclonal antibody-defined tumor markers: CA 19-9, CA 50 and CA 125. Tumor Biol. 7, 333, 1986.
45. MADIYALKAN R., PISKORZ C. F., PIVER S. and MATTA K. L.: Serum β(1–4)-galactosyltransferase · activity with synthetic lower molecular weight acceptor in human ovarian cancer. Eur. J. Cancer clin. Oncol. 23, 901, 1987.
46. HEINONEN P. K., KOIVULA T. and PYSTYNEN P.: Decreased serum level of dehydroepiandrosterone sulfate in postmenopausal women with ovarian cancer. Gynec. Obstet. Invest. 23, 271, 1987.
47. CANNEY P. A., WILKINSON P. M., JAMES R. D. and MOOR M.: CA 19-9 as a marker for ovarian cancer: alone and in comparison with CA 125. Br. J. Cancer 52, 131, 1985.
48. SPONA J., GITSCH E., SALZER H. and KARRER K.: Estrogen- and Gestagen-receptors in ovarian carcinoma. Gynec. Obstet. Invest. 16, 189, 1983.

49. TATRA G., GRING H., LASNIK E. and WASCHER C.: Studies of β-2-microglobulin in patients with gynaecological tumors. Tumor diag. Ther. 7, 116, 1986.

50. WEED J. C., WOODWARD K. T. and HAMMOND C. B.: Chorioncarcinoma metastatic to the brain: therapy and prognosis. Sem. Oncol. 9, 208, 1982.

51. LURAIN J. R., BREWER J. I., TOROK E. E. and HALPERN B.: Gestational trophoblastic disease: treatment results at the Brewer Trophoblastic Disease Center. Obstet. Gynec. 60, 354, 1982.

52. BAGSHAWE K. D., WASS M. and SEARLE F.: Markers in gynaecologic cancer. Archs Gynec. 229, 303, 1980.

53. ZARATE A. and MACGREGOR C.: Beta-subunit HCG and the control of trophoblastic disease. Sem. Oncol. 9, 187, 1982.

54. ANDERSON T., WALDMANN T. A., JAVADPOUR N. and GLATSTEIN E.: Testicular germ cell neoplasms, recent advances in diagnosis and therapy. Ann. intern. Med. 90, 373, 1979.

55. GOLDHIRSCH A. and ALMENDRAL A. C.: Maligne gynäkologische Tumoren (Genital-Karzinome), in BRUNNER K. W. and NAGEL G. A. (eds): Internistische Krebstherapie, p. 388. Berlin, Springer, 1985.

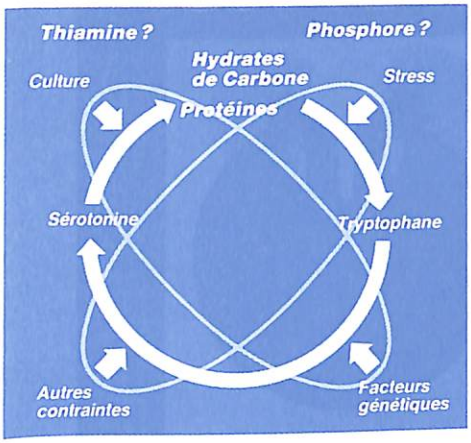
56. BAGSHAWE K. D.: Trophoblastic disease, in CAPLAN R. M. and SWEENEY W. J. (eds): Advances in Obstetrics and Gynecology, p. 225. Baltimore, Williams and Wilkins, 1987.

57. HAMMOND C. B., WEED J. C. and CURRIER J. L.: The role of operation in current therapy of gestational trophoblastic disease. Am. J. Obstet. Gynec. 136, 844, 1980.

Le choix des aliments, une réalité biologique aujourd'hui mieux connue.

La pulsion, l'attirance impérieuse vers la nourriture, et plus particulièrement les aliments glucidiques (aliments sucrés, féculents...), est restée jusqu'à ces dernières années un phénomène mystérieux.

Nous savons aujourd'hui que la prise de glucides induit au niveau du système nerveux central une activation sérotoninergique très spécifique, dont dépend, entre autres, le choix des aliments lors du repas suivant.



La découverte de cette voie neurophysiologique spécifique a permis de comprendre comment l'organisme assure, par compensation successive, d'un repas à l'autre, l'ajustement de ses besoins glucido-protidiques, et donc l'équilibre nutritionnel nécessaire au maintien du meilleur état de santé possible.

La rupture de cet équilibre peut conduire à une véritable anarchie avec prises alimentaires compulsives, non régulées, en dehors des repas. C'est dire tout l'intérêt d'avoir testé l'effet d'un agent sérotoninergique tel Isoméride sur les pulsions alimentaires induites par le stress ou les pulsions alimentaires glucido-dépendantes.

Dans la surcharge pondérale

ISOMERIDE

DEXFENFLURAMINE

2 gélules par jour

PROPRIÉTÉS

Pharmacodynamique

L'ISOMERIDE agit sur la régulation centrale de la prise de nourriture.

L'ISOMERIDE a un mécanisme d'action sérotoninergique qui sous-tend son activité pharmacodynamique. L'ISOMERIDE inhibe la recapture, et augmente la libération de sérotonine.

Chez l'animal, il a été démontré que l'ISOMERIDE possède une action sélective sur les comportements alimentaires susceptibles d'induire une obésité :

- en inhibant électivement la consommation de glucides tout en respectant la consommation de protéines,
- en inhibant l'hyperphagie induite par l'insuline,
- en inhibant l'hyperphagie de situation anxiogène.

Chez l'homme, dans l'obésité avec trouble du comportement alimentaire (compulsion pour les hydrates de carbone) l'ISOMERIDE inhibe de façon sélective la consommation de glucides et diminue ainsi la consommation calorique globale, tout en respectant la prise de protéines.

L'ISOMERIDE se différencie radicalement des anorexigènes amphétaminiques

- absence d'effet psychostimulant
- absence d'effet hypertenseur
- absence de potentiel d'addiction.

Pharmacocinétique

Après administration orale, l'absorption de l'ISOMERIDE est pratiquement complète. Le pic de concentration plasmatique est atteint 4 heures après la prise de 30 milligrammes.

En administration répétée, à dose thérapeutique, une gélule le matin et une gélule le soir, l'état d'équilibre est atteint vers le quatrième jour et reste stable à la concentration moyenne de 40 ng/ml.

La liaison aux protéines plasmatiques est faible (36 pour cent).

Le produit est fortement métabolisé avec formation entre autres de d-norfenfluramine qui participe à l'activité globale du produit. Aucun dérivé de l'amphétamine n'a été mis en évidence. La clearance plasmatique est de 45 litres par heure. L'élimination est presque exclusivement urinaire, plus de 90 pour cent de la dose étant recueillis en 3 à 4 jours par cette voie. Le temps de demi-vie d'élimination est d'environ 18 heures pour la d-fenfluramine et 40 heures pour la d-norfenfluramine.

INDICATIONS

En association avec le régime, traitement de l'obésité simple, de l'obésité compliquée de l'adulte, de l'obésité réfractaire et de l'obésité avec trouble du comportement alimentaire (compulsion pour les hydrates de carbone) lorsque les mesures diététiques ne sont pas suffisantes.

POSOLOGIE ET MODE D'EMPLOI

2 gélules par jour, à savoir une gélule le matin et une gélule le soir, de préférence au cours des repas.

En principe, la durée de traitement est limitée à 3 mois.

CONTRE-INDICATIONS

- Glaucome, antécédents d'anorexie mentale, antécédents dépressifs, antécédents psychiatriques, propension aux abus médicamenteux, alcoolisme avéré.
- Du fait du mécanisme d'action sérotoninergique de l'ISOMERIDE, l'association aux I.M.A.O. est contre-indiquée (un intervalle d'au moins 15 jours doit être respecté).

EFFETS INDÉSIRABLES

- Les plus fréquemment rapportés sont : sécheresse de la bouche, nausées, constipation, diarrhée. Ces effets cèdent à la poursuite du traitement.
- Ont été plus rarement observés : somnolence, étourdissement, pollakiurie, céphalée, asthénie, trouble de l'humeur, dépression réactionnelle, insomnie, nervosité.

PRÉCAUTIONS PARTICULIÈRES

- Les causes organiques d'obésité doivent être éliminées avant la prescription de ce produit.
- Ce produit doit être utilisé avec précaution chez les sujets présentant des troubles du rythme.
- En l'absence de données spécifiques chez les insuffisants hépatiques et/ou insuffisants rénaux, l'administration de ce produit devra être évitée chez de tels patients.

GROSSESSE ET LACTATION

L'ISOMERIDE n'est pas tératogène et n'altère pas la reproduction chez l'animal.

Cependant, l'usage de l'ISOMERIDE au cours des 3 premiers mois de la grossesse doit être évité.

Pendant la période de lactation, il est déconseillé d'utiliser l'ISOMERIDE même si aucun effet n'a été observé chez l'animal.

INTERACTIONS

- Ne pas associer à un autre anorexigène à action centrale ni à un I.M.A.O. (cf. contre-indications)
- Ce produit peut potentialiser :
  - les médicaments dépresseurs du système nerveux central (sédatifs)
  - les antihypertenseurs
  - les effets hypotenseurs des antidépresseurs tricycliques
  - les sulfamides hypoglycémiants

CONDUITE D'UN VÉHICULE ET UTILISATION DE MACHINES

L'ISOMERIDE peut induire une sédation chez certains patients ; les conducteurs de véhicules et les utilisateurs de machines doivent en être avertis.

L'absorption simultanée d'alcool ou de médicaments dépresseurs du système nerveux central peut potentialiser cet effet de sédation.

SURDOSAGE

- Peu de données sont disponibles sur les accidents de surdosage.
- Le traitement d'urgence comporte :
  - un lavage d'estomac,
  - une diurèse forcée avec acidification des urines pour accélérer l'excrétion du produit,
  - une réanimation avec surveillance cardiaque dans les cas les plus sévères.

CONSERVATION

A température ambiante (15-25° C)

Stabilité

La date de péremption est indiquée sur la boîte. Les deux premiers chiffres indiquent le mois et les seconds chiffres indiquent l'année de péremption ; la date de péremption est toujours le premier jour du mois indiqué.

DÉLIVRANCE

Délivré sur prescription médicale.

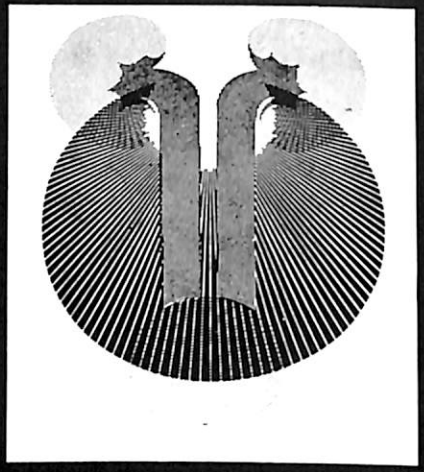
Présentation

60 gélules sous plaquettes thermoformées.

SERVIER BENELUX S.A.
BD E. BOCKSTAEL 93 1020 BRUXELLES

Harnweginfekte

kompromisslos und spezifisch behandeln



Urospasmon®

Hohe Erregerempfindlichkeit bei geringem Risiko – daher auch bei Banalinfekten einsetzbar

Urospasmon®

besonders geeignet zur Behandlung des schmerzhaften Infekts

Urospasmon® sine

besonders angezeigt beim chronischen Infekt und zur Langzeittherapie

Indikationen: Akute und chronische Harnweginfektionen, Pyelonephritis, zur Infektionsprophylaxe bei diagnostischen und operativen Eingriffen in der Urologie
Kontraindikationen: Eingeschränkte Nierenfunktion mit erhöhten Rest-N-Werten, Oligurie, Anurie, Uramie, Polyneuropathie, Sulfonamid- und Nitrofurantoin-Überempfindlichkeit, schwere Leberparenchymschaden. Anwendung während der ersten 3 Lebensmonate. Keine hexamethylentetraminhaltigen und zusätzlich bei UROSPASMON keine schwefel- und quecksilberhaltigen Präparate gleichzeitig verabreichen
Mögliche Nebenwirkungen: Gastrointestinale Störwirkungen, Kopfschmerzen, Allergien, Fieberschübe, Exanthem, Cholestase, pulmonale Reaktionen, anaphylaktische Erscheinungen, Anämien, Paraesthesien
Hinweise: Um die erforderliche tägliche Harnmenge von 1,5 l zu gewährleisten, ist es zweckmäßig, eine Durchspülungstherapie mit SOLUBITRAT (Basis-Information umseitig) durchzuführen, das kein Hexamethylentetramin enthält. Weitere Informationen enthalten die wissenschaftlichen Prospekte.

Urospasmon®

Zusammensetzung:
1 Tablette: Nitrofurantoin 50 mg, Sulfadiazin 150 mg, Phenazopyridin 50 mg

Handelsformen
20 Tabletten
50 Tabletten
Anstaltspackungen

Urospasmon® sine

Zusammensetzung:
1 Kapsel: Nitrofurantoin 50 mg, Sulfadiazin 150 mg

Handelsformen
20 Kapseln
50 Kapseln
Anstaltspackungen

Urospasmon® sine pro infantibus

Zusammensetzung:
1 Kapsel: Nitrofurantoin 12,5 mg, Sulfadiazin 37,5 mg

Handelsform
50 Kapseln
Anstaltspackung

Stand Mai 1978

HEUMANN Arzneimittel
NÜRNBERG

Littérature et échantillons: Comptoir Pharmaceutique Luxembourgeois S.A., Luxembourg

Residual Tumor Cells

Abnormal in vitro Differentiation of Clonogenic B-cells in Common Acute Lymphoblastic Leukemia in Complete Remission. A Marker for Minimal Residual Disease?

J. Bréard, G. Mathé and R. Consolini

Abstract

An in vitro B-cell colony assay system was used to evaluate B-cell differentiation from peripheral blood precursors in common acute lymphoblastic leukemia (cALL) patients in remission as compared to normal controls. Significant differences in the morphologic and phenotypic features of pooled colony cells were found between the two groups. The morphology and surface markers of control-cultured cells were those of young plasmocytes. In contrast, patients' cells had predominantly a lymphoblastoid appearance and a mean of 18% (2–72%) of the cells expressed the cALL (CALLA) antigen. This marker, known to be present on normal pre-B-cells and malignant cALL cells, was not found on control colony cells. Cytogenetic studies performed in four cases showed that a fraction of the patients' colony cells had karyotypic abnormalities similar to that of the original lymphoblasts. These data suggest that the cells with immature features persisting in the colonies of cALL patients are the progeny of residual circulating cells linked to the malignant clone which cannot be detected in the fresh sample and are clonally expanded during the culture.

INTRODUCTION

The CALLA antigen, originally described by Greaves (1) on the surface of cALL lymphoblasts is not leukemia specific since it can be found on a variable fraction of normal bone marrow cells (2,3) and on some non-lymphoid cells (4,5). Within the hematopoietic lineage, CALLA is considered to be a normal differentiation antigen, and its expression by early B-cells, both normal and malignant, correlates with the recent evidence that most cALL blasts belong to the B-lineage (6–10).

The present study was initiated by our finding that a small percentage of cells expressing the CALLA antigen could be detected in the peripheral blood of some cALL patients in remission receiving maintenance chemotherapy (11). As

SMST and ICIG (CNRS UA 041163)
Hôpital Paul-Brousse,
94800 Villejuif, France

CALLA+ cells are usually not detectable in the blood of healthy subjects, we wondered whether we were detecting residual leukemic cells or normal immature cells released inappropriately in the patients' blood. As the very low number of such cells precluded the determination of their nature, we used a recently described technique that permits the generation of B-cell colonies from both normal and malignant progenitors (12). Our aim was thus to induce in vitro the clonal expansion and differentiation of B-lineage cells in these patients and to study the features of the colony cells at the end of the culture. The results of this study have been recently published in detail (11) and will be summarised here.

PATIENTS AND METHODS

A total of 20 cALL and five T-ALL patients in remission submitted to a similar maintenance chemotherapy protocol, two acute myloid leukemia patients and seven normal donors were studied. Complete remission was checked in all cases by standard clinical and hematologic criteria. The B-cell colony assay was directly adapted from that described by Izaguirre et al. (12) and applied to the E rosette negative fraction of peripheral blood mononuclear cells. At the end of the culture, the morphology and the surface markers of the colony cells were examined, the latter being performed by indirect immunofluorescence using monoclonal antibodies directed against the CALLA antigen (J5), the B-cell antigen B1 and the Ia antigen. Chromosome analysis was performed for the colony cells of four patients for whom chromosomal abnormalities had been detected in the original lymphoblasts, using the GTG banding technique (13).

BONE MARROW AND PERIPHERAL BLOOD CALLA+ CELLS

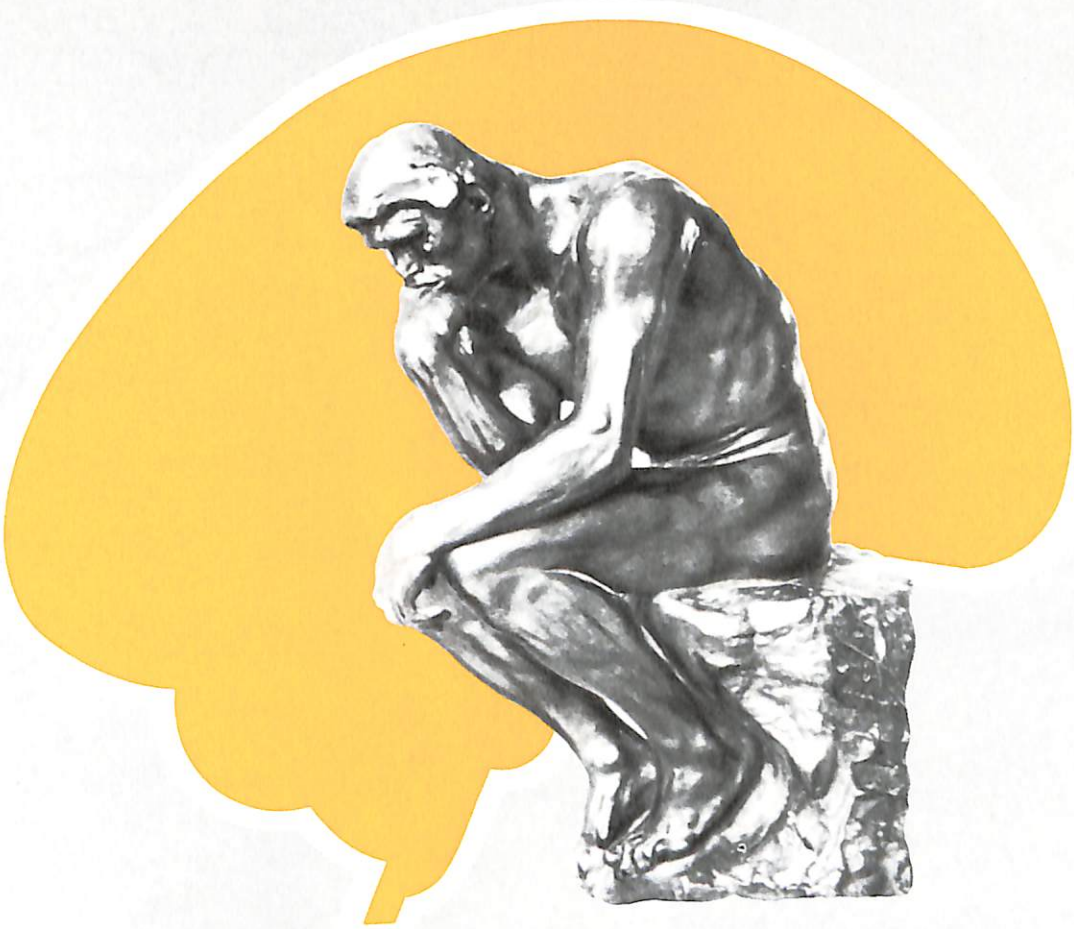
The percentage of CALLA+ cells in fresh bone marrow and peripheral blood samples was studied for the 20 cALL patients. In the bone marrow, this percentage ranged from 0 to 12% and was above 5% in four patients. Bone marrow cellularity was normal in these cases, with no evidence of lymphocytosis. The proportion of CALLA+ cells in the peripheral blood of these 20 patients was 0–3% and reached 15% in only one case. Peripheral blood cells from the five T-ALL, the two AML and the seven healthy volunteers were CALLA negative, except for one T-ALL patient who had 2% circulating CALLA+ cells.

CALLA+ CELLS IN cALL PATIENTS' B-CELL COLONIES

Peripheral blood mononuclear cells were depleted of T-lymphocytes by E rosette formation and the non-T-cell fraction was cultured in methyl cellulose, under conditions which induce the growth of B-cells colonies. At the end of the 6 days culture, the colonies were counted, the cells were pooled, and the morphology and surface markers of pooled cells was studied. The results are summarised in Table 1. As can be seen, control-cultured cells had no receptor for SRBC, most were Ig+ and 25% bore the Ia antigen. Moreover, in both subjects which were also tested with the monoclonal antibody anti-B1, 40% and 58%, respectively, of the colony cells were found to express this B-cell-specific antigen (not shown). The morphological features of the colony cells, studied after Wright–Giemsa staining, were those of plasmacytoid cells. These results demonstrate that the culture system used here induces the specific growth of B-lineage cells.

The assay was technically satisfactory for 15 of the 20 cALL patients, and the presence of surface Ig and B1 antigen (two cases studied, not shown) confirmed the B-cell nature of most of the patients colony cells. A major difference with normal subjects, however, was that a mean of 18% (range 2%–72%) expressed the CALLA antigen. Moreover, a fraction of the patients' cultured cells had a plasmacytoid appearance. Both criteria therefore seemed to indicate that the colony cells were less differentiated in the patients cultures than in the controls. The mature phenotype of the T-ALL and AML cases colony cells made it unlikely that the chemotherapeutic regimen was affecting the differentiation of B-cells in cALL patients. It appeared therefore that, for these patients, some of the circulating B-cells were unable to mature in vitro beyond the differentiation stage corresponding to that of the original tumor.

Dans les troubles de la mémoire.



OXYGERON

Stimule

- le métabolisme
- l'hémodynamie
- la rhéologie
- les neurotransmetteurs impliqués dans la senescence cérébrale

Composition: Vincamine - Retard 30 mg.
Indications: Insuffisance cérébrale - Ischémie cérébrale - Troubles vasculaires de la région optique - Migraines - Céphalées - Vertiges.
Contre-indications: Grossesse.
Effets secondaires: Rares cas de nausées et rougeurs de la face.
Précautions: Ne pas croquer les microgranules.
Posologie: 1 gélule matin et soir.

Délivré sur ordonnance médicale..

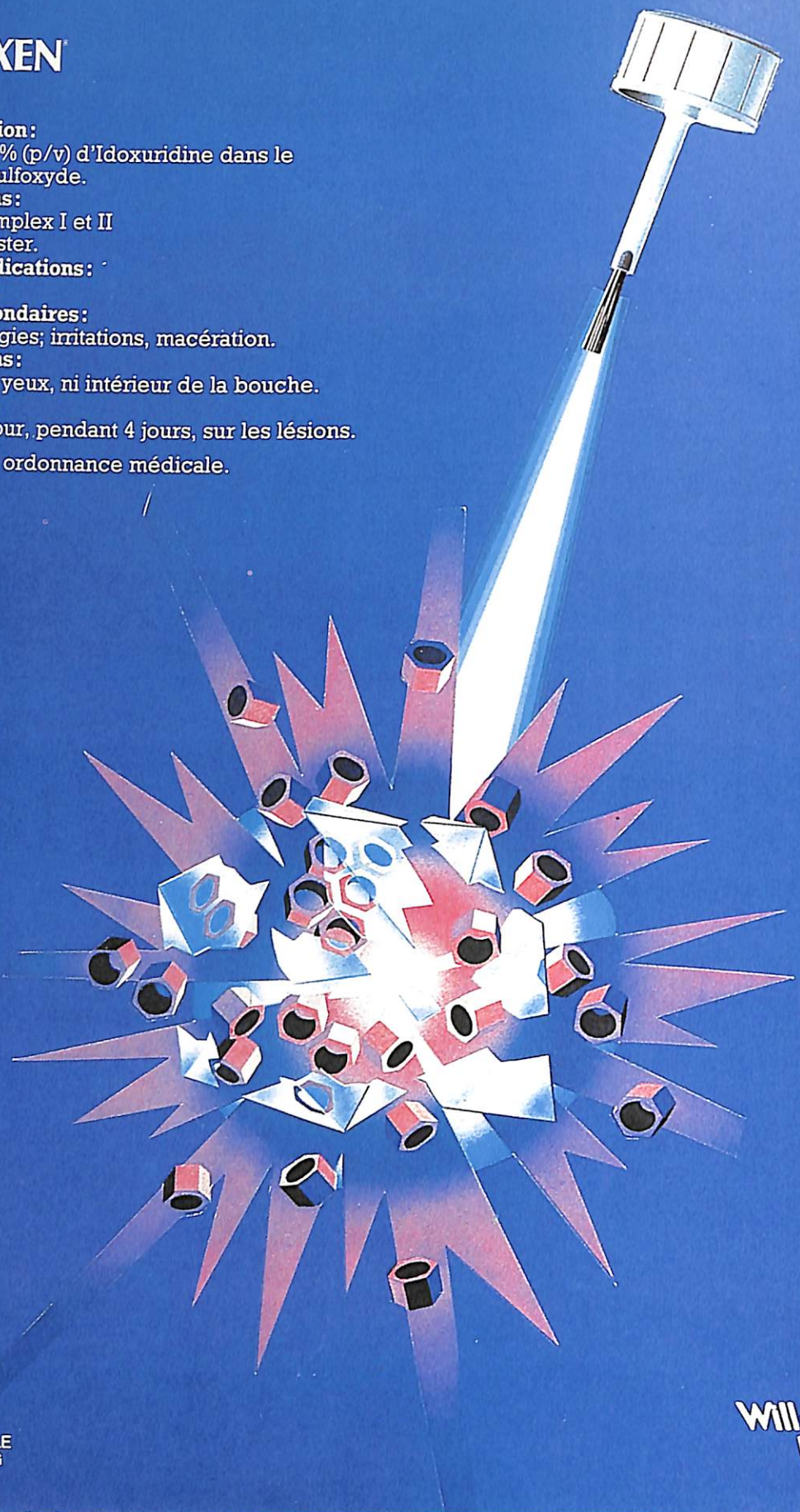
Will-Pharma luxembourg

rue d'Anvers 35 Luxembourg-Ville

VIREXEN®

Composition:
10% ou 40% (p/v) d'Idoxuridine dans le dimethylsulfoxyde.
Indications:
Herpes Simplex I et II
Herpes zoster.
Contre-indications:
grossesse.
Effets secondaires:
Rares allergies; irritations, macération.
Précautions:
Pas sur les yeux, ni intérieur de la bouche.
Posologie:
4 fois par jour, pendant 4 jours, sur les lésions.

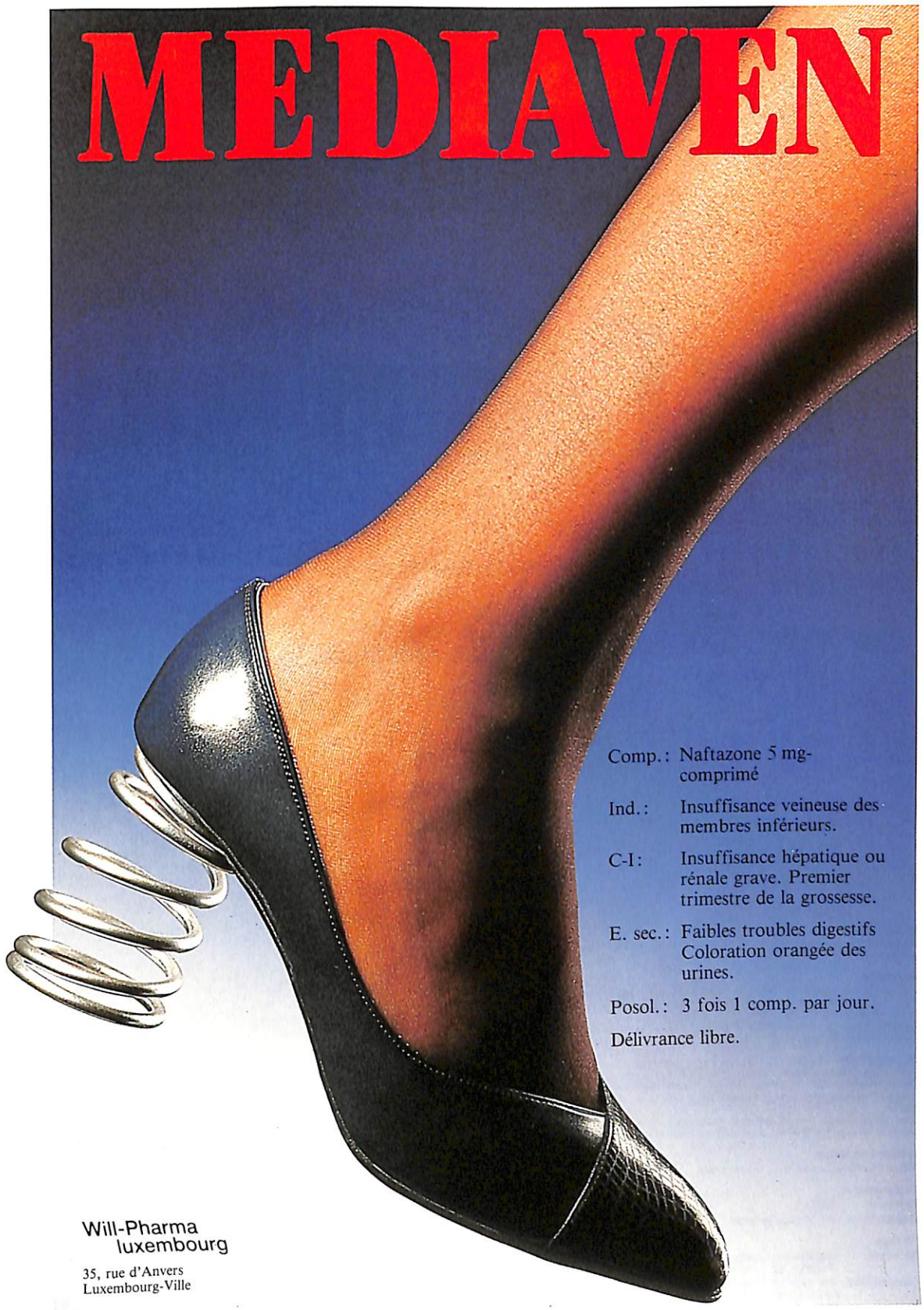
Délivré sur ordonnance médicale.



e d'Anvers
MBOURG-VILLE
LUXEMBOURG

Will-Pharma
luxembourg

MEDIAVEN



Comp.: Naftazone 5 mg-comprimé

Ind.: Insuffisance veineuse des membres inférieurs.

C-I: Insuffisance hépatique ou rénale grave. Premier trimestre de la grossesse.

E. sec.: Faibles troubles digestifs Coloration orangée des urines.

Posol.: 3 fois 1 comp. par jour.

Délivrance libre.

Will-Pharma
luxembourg

35, rue d'Anvers
Luxembourg-Ville

hémorroïdes

triAnal®

Pommade - Suppositoires

triamcinolonacetonide et lidocaine HCl

Indications:
Hémorroïdes externes et internes, eczéma anal, prurit anal, traitements pré- et postopératoires.

Propriétés:
Le triAnal, en suppositoires et en pommade, est indiqué pour le traitement des douleurs hémorroïdales aiguës ainsi que pour les inflammations et le prurit de la région anale.
Le triAnal hâte la régression de la douleur, des démangeaisons et des phénomènes inflammatoires.

Mode d'emploi:
Suivant la gravité du cas: 1 suppositoire, 1 à 2 fois/jour ou 2 à 4 applications de pommade/jour, sur la partie cutanée irritée ou sur les hémorroïdes externes.
En cas d'hémorroïdes internes situées profondément, on utilisera les suppositoires.
Afin de permettre une introduction hygiénique de ceux-ci, 10 doigtiers sont joints à l'emballage (des suppositoires seulement).

Contre-indications:
Processus tuberculeux de la région anale.

Présentations:
Pommade: 1 x 20 g
Suppositoires: 1 x 10 suppositoires

Formula:
Pommade: Triamcinolon. acetonid. 0,25 mg – Lidocain. hydrochlorid. 50 mg. - Paraffin. liq. – Polyethylen. q. s. ad. 1 g
Suppositoires: Triamcinolon. acetonid. 0,5 mg – Lidocain. hydrochlorid. 50 mg. – Adeps synth. dérog. – n° 42/615. – Adeps solidus q. s. pro supposit. uno.

Délivré sur ordonnance médicale.

Will-Pharma
luxembourg

Rue d'Anvers 35 - Luxembourg-Ville
G.D. Luxembourg
Tél.: 48.83.60

TABLE 1. Phenotypic characterisation of pooled colony cells in controls and in cALL and T-ALL patients

Cell fraction	Controls E− (n=7)	Controls E-J5− (n=7)	cALL patients E− (n=15)	cALL patients E-J5− (n=11)	T-ALL patients E− (n=5)
Colonies/ 10^5 cells	354 ± 260	268 ± 145	628 ± 526	858 ± 891	357 ± 115
% Positive cells for:					
E rosettes	4 ± 2	6 ± 2	6 ± 4	8 ± 3	4 ± 1
Surface Ig	67 ± 6	65 ± 9	57 ± 6	57 ± 3	65 ± 3
Ia antigen	25 ± 8	22 ± 6	43 ± 11	34 ± 13	28 ±9
J5 antigen	0.2 ± 0.4	0.3 ± 0.5	18 ± 19	17 ± 18	0.5 ± 0.3

After obtention of these results, we wondered whether the cALL+ colony cells were the progeny of the few circulating CALLA+ cells occasionally found in the fresh blood samples. The E rosette negative cells were therefore incubated with the J5 antibody in the presence of rabbit complement prior to the culture. As can be seen in Table 1, prior lysis of J5+ cells did not alter significantly either the plating efficiency or the phenotype of the cultured cells suggesting that CALLA+ cells can be generated in vitro from CALLA− progenitors.

As was the case for circulating CALLA+ cells, we wondered whether we were detecting a lack of differentiation of normal B-cells or the presence of malignant cells in the patients colonies. We tried to answer this question by performing two types of experiments: the study of the self-renewal capacity, and of the karyotype of the colony cells.

PROPERTIES OF B-COLONY CELLS OF cALL PATIENTS

The clonogenic capacity of B-colony cells from cALL patients and controls was investigated by pooling and replating the primary colonies. A significant secondary plating efficiency was observed in four of four patients studied and the proportion of J5+ cells was comparable to that found in the primary cultures (not shown). In contrast, secondary plating efficiency in controls was very low (not shown). Thus, some of the patients' colony cells are capable of self-renewal, a property usually associated with stem cells and malignant cells.

The karyotype of the cultured cells was studied in four patients for whom chromosomal abnormalities had been found in the original lymphoblasts. In all four cases, a fraction of the cultured cells presented chromosomal aberrations identical to that found in the initial corresponding lymphoblasts. It thus appeared that, despite complete hematologic remission, these patients had in their peripheral blood residual cells belonging to the malignant clone. The expansion of these circulating precursors during culture allowed the detection of their abnormal progeny by classic cytogenetic methods. Since chromosome examination and study of surface markers could not be performed on the same cells, we do not know the phenotypic features of the colony cells with chromosomic aberrations. It should, however, be noted that in all cases the percentage of J5+ cells and the number of abnormal metaphases in the colonies were comparable. However, further work is needed to establish whether the abnormal clonal cells express the J5 determinant.

CLINICAL OBSERVATIONS

The clinical course of the patients will also be important in understanding the significance of these findings, by indicating whether a correlation between percentage of CALLA+ cells and an eventual relapse can be established. During this study, three patients relapsed 1, 5 and 2 months after being studied. The pro-

portion of J5+ cells in the colonies was 50%, 72% and 13%, respectively. The first and the third patient had virtually no CALLA+ cells in their blood or bone marrow at the time of study. Moreover, no patient in the group of less than 5% CALLA+ colony cells has relapsed thus far.

CONCLUSION

We have shown that some circulating B-clonogenic cells of C-ALL patients in remission do not differentiate in vitro under experimental conditions that allow the maturation of normal B-cells. The self-renewal capacity of some of these cells, the presence of an identical karyotypic abnormality in some cultured cells and in the original lymphoblasts, and the subsequent relapse of three patients who had a relatively high proportion of J5+ colony cells seems to indicate that this culture system permits the clonal expansion of residual circulating cells linked to the malignant clone. This observation might be of biologic as well as clinical importance, since these residual cells cannot be detected by classic hematologic, cytologic or even immunologic methods.

REFERENCES

1. GREAVES M. F., BROWN G., RAPSON N. T. and LISTER A.: Clin. Immun. Immunopath. 4, 67, 1975.
2. JANOSSY G., BOLLUM F. J., BRADSTOCK K. F., MCMICHAEL A., RAPSON N. and GREAVES M. F.: J. Immun. 123, 1525, 1979.
3. GREAVES M., DELIA D., JANOSSY G., RAPSON N., CHESSELS J., WOODS M. and PRENTICE G.: Leuk. Res. 4, 15, 1980.
4. METZGAR R. S., BOROWITZ M. J., JONES N. H. and DOWELL B. L.: J. exp. Med. 154, 1249, 1981.
5. KEATING A., WHALEN C. K. and SINGER J. W.: Br. J. Haemat. 55, 623, 1983.
6. KORSMEYER S. J., HIETER P. A., RAVETH S. V., POPLOCK D. G., LEDER P. and WALDMAN T. A.: in KNAPP W. (ed.): Leukemia Markers, p. 85. New York, Academic Press, 1981.
7. GREAVES M. F., VERBI W., KEMSHEAD J. and KENNET R.: Blood 56, 1141, 1980.
8. NADLER L. M., RITZ J., REINHERZ E. L. and SCHLOSSMAN S. F.: in KNAPP W. (ed.): Leukemia Markers, p. 3. New York, Academic Press, 1981.
9. NADLER L. M., RITZ J., BARES M. P., PARK E. K., ANDERSON K. C., SALLAN S. E. and SCHLOSSMAN S. F.: J. clin. Invest. 70, 433, 1982.
10. COSSMAN, NECKERS L. M., ARNOLD A. and KORSMEYER S. F.: New Engl. J. Med. 307, 1251, 1982.
11. CONSOLINI R., BREARD J., BOURIN-BAIAR A., GOUTNER A., GEORGOULIAS V., CANON C., BRUGERIE E. and MATHÉ G.: Blood 67, 786, 1986.
12. IZAGUIRRE C. A., CURTIS J., MESSNER H. and MCCULLOCK E. A.: Blood 57, 823, 1981.
13. DUTRILLAUX B.: Monographie des Annales de Génétique. Paris, L'Expansion Scientifique, 1975.

Identification of Mammary Metastatic Cells in the Bone Marrow as a Marker of a Minimal Residual Disease and of their Proliferative Index as a Factor of Prognosis—an Immunocytologic Study with Monoclonal Antibodies

M. Ginsbourg, M. Musset, J. L. Misset, O. Genty and G. Mathé

Abstract

A study of 200 patients with breast cancer at different stages was carried out. Proliferating mammary cells in bone marrow were detected using a double-staining method with monoclonal antibodies. Mammary cells were visualized with antibodies raised against human breast tissue or carcinoma. DNA-synthetising cells (S-phase) were detected on the same slide, using the monoclonal antibody antibromodeoxyuridine (BrdU), after cell incubation with BrdU.

Mammary cells could be detected in the bone marrow of 60% of the studied cases. In 50% of the samples with such 'micrometastasis', a high labelling index of the carcinoma cells was found. The correlation between the presence of micrometastasis and the general prognosis at the stage of residual disease is discussed.

INTRODUCTION

Bone marrow is a site for metastasis of many epithelial carcinomas. Morphologic studies of Romanowsky-stained bone marrow smears allow identification of metastatic cells in advanced disease. More often, however, bone marrow infiltration with a few cells is undetected with routine studies (1).

Recent techniques in tumor immunology and hybridoma technology have provided a new tool in the study of carcinomas. Monoclonal antibodies permit the specific demonstration of cell and tissue antigens. Micrometastases containing only a few tumor cells are detected in one-third of bone marrow smears obtained from early disease (2).

The present study describes the findings of a double-labelling procedure of isolated bone marrow cells for the simultaneous detection of breast carcinoma-associated antigen and DNA synthesis after culture with a precursor visualised by a monoclonal antibody (3). Detection of DNA-synthetising tumor cells in patients with no detectable metastasis will be correlated with prognosis in a follow up study.

Service des Maladies Sanguines et Tumorales & ICIG (Université Paris-Sud, CNRS UA 04-1163), Hôpital Paul-Brousse, 94800-Villejuif, France

MATERIAL AND METHODS

Bone marrow samples

Bone marrow samples were obtained from patients with breast cancer at presentation (20 cases), after surgery (160 cases), and from patients with breast cancer metastasis (20 cases).

Control samples were obtained from patients with leukemia in remission (ten cases), with plasmocytoma (two cases), and with ovarian or colon carcinoma (four cases).

Reagents

RPMI 1640 culture medium was obtained from Gibco (U.S.A.) and foetal calf serum from Biopro (France). Bromodeoxyuridine was purchased from Sigma (U.S.A.). Anti-BrdU monoclonal antibody was obtained from Becton-Dickinson (U.S.A.) and anti-breast tissue monoclonal antibody was obtained from Australian Monoclonal Development (Australia) and from Biogenex (U.S.A.). Monoclonal antibody raised against milk fat globule membrane was kindly supplied by Dr Munro- Neville (Ludwig Institute, England) (Table 1).

Cell isolation

Heparinised bone marrow aspirates were processed for cell separation by Ficoll–Hypaque® gradient separation. After washing, mononuclear cells together with the supernatant were collected and eluted to 1×10^6 cells per ml.

Cell culture for kinetic study

BrdU, an analogue of thymidine, is incorporated only in DNA of cells undergoing DNA synthesis. $1-5 \times 10^6$ cells resuspended in one milliliter RPMI 1640 medium supplemented with 10% fetal calf serum and antibodies, were incubated with BrdU, 10 μ M for 30 minutes, in a CO_2 incubator at 37°C. the incubation was stopped in an ice bath.

Cytocentrifuged slides of the labelled cells were stored at room temperature for a few days, or at −20°C if staining was to be delayed.

Immunofluorescence staining

Staining was performed with two monoclonal antibodies labelled with different fluorochromes to localise both antigens simultaneously in one cell.

Indirect immunofluorescence staining was first performed for detection of breast tissue-associated antigen with 1/10 diluted monoclonal antibody, at room temperature, for 30 minutes, in a humidified chamber. After washing, sheep antimouse Ig-TRITC conjugate was used as a second step antibody. Incubation was performed at room temperature for 20 minutes. After washing, direct immunofluorescence was performed using anti-BrdU fluoresceine-conjugate monoclonal antibody for DNA-synthesising cell detection.

After washing and mounting, fluorescence was observed by fluorescence microscopy with adapted filters.

Cells reacting with the antibody against breast tissue present a red fluorescence located on the cell surface or in the total or partial cytoplasmic area. DNA-synthesising cells present green spots located in the nuclear

TABLE 1. Monoclonal antibodies used for immunofluorescence staining of isolated bone marrow cells

Antibody	Reference	Antigen	Tissue or cell distribution
Licrlon M8	Foster et al. (6)	Human milk fat globule membrane	Subsets of luminal epithelial cells
Hu Tu M1	Thompson et al. (10)	Epithelial membrane antigen	Specific for breast tissue: breast carcinoma and normal breast
MA05—5C	Histogen®	Tumor associated cell surface antigen	Breast carcinoma. This antibody reacts with many epithelial tumors but is unreactive with normal cells
AntibrdU	Gratzner (3)	Bromodeoxyuridine	DNA-synthesising cells

duphar

DUPHAR & Cie S.N.C.
BD. EMILE BOCKSTAEL 122 - 1020 BRUXELLES
TEL. 02/428.00.50

betaserc®

bifiteral®

dihydral®

duphalac®

duphaston®

duspatalin®

duspatalin® liquid

duvadilan® retard

fiberform®

flammacerium®

flammazine®

floxyfral®

influvac® S

pre-par®

neo dohyfral®

AD-lets

Rantudil®

NEU von Tropon **retard** **Gegen Rheuma**

Wirkung: stark – Verträglichkeit: sanft

Wenn der Schmerz im Vordergrund steht.

Rantudil® forte

Wenn die chronischen Beschwerden dominieren.

Rantudil® retard

Zusammensetzung: 1 Kapsel Rantudil enthält 30 mg Acemetacin, 1 Kapsel Rantudil forte enthält 60 mg Acemetacin, 1 Kapsel Rantudil retard enthält 90 mg Acemetacin. Indikationen: Chronischer Gelenkrheumatismus, Psoriasis-Arthritis, aktivierte Arthrose/Spondylarthrose, M. Bechterew, Gichtanfall, Entzündungen der Gelenke, Muskeln, Sehnen und Schleimbeutel, chronische Lumbago-Ischialgie, posttraumatische/postoperative Entzündungen und Schwellungen, Thrombophlebitis und Vasculitis. Kontraindikationen: Überempfindlichkeit gegen Acemetacin, Acetylsalicylsäure, Indometacin und andere nichtsteroidale Entzündungshemmer sowie Neigung zu Überempfindlichkeit infolge Asthma, Heuschnupfen, Nasenschleimhautschwellungen oder chronischen Atemwegsinfektionen. Vorausgegangenes oder bestehendes Magen- oder Zwölffingerdarmgeschwür (ausgenommen unter strenger ärztlicher Kontrolle). Sorgfältige Überwachung bei schwerer Leber-, Nieren- oder Herzinsuffizienz bzw. stark erhöhtem Blutdruck. Schwangerschaft, Stillzeit und Kinder unter 14 Jahren. Nebenwirkungen: Magen-Darm-Störungen sind möglich, gelegentlich Kopfschmerzen oder Schwindelgefühl, selten Augenflimmern, vorübergehende Beeinträchtigung des Sehvermögens, Ohrenklingen, Müdigkeit, allergische Reaktionen, sehr selten pektanginöse Beschwerden, Ödeme, Magen-Darm-Geschwüre (z. T. mit Blutungen) sowie Leberfunktionsstörungen (u. U. mit Gelbsucht). Dieses Arzneimittel kann auch bei bestimmungsgemäßem Gebrauch das Reaktionsvermögen so weit verändern, daß die Fähigkeit zur aktiven Teilnahme am Straßenverkehr oder zum Bedienen von Maschinen beeinträchtigt wird, verstärkt im Zusammenwirken mit Alkohol. Handelsformen: 20 Rantudil Kapseln; 50 Rantudil Kapseln; 20 Rantudil forte Kapseln; 50 Rantudil forte Kapseln; 20 Rantudil retard Kapseln; 50 Rantudil retard Kapseln. Tropon Arzneimittel Köln.

Rheuma-Forschung

Für Luxembourg: Integral S. A., 5, Rue Christophe-Plantin, Téléphone 48.56.56

– rezeptpflichtig –

area. The anti-breast antibody staining pattern was identical for the three antibodies used (anti-breast Australia and Biogenex, anti-milk fat globule).

Non-specific staining of granulocytic cells was eliminated by preincubation at 37°C and by use of Fab-Ig fragment as second antibody. Non-specific staining of eosinophilic granulocytes was prevented by pretreatment with diaminobenzidine and H_2O_2 (4).

RESULTS

Details of the immunofluorescence labelling data are shown in Table 2. Of 16 samples obtained from patients without known breast carcinoma, immunofluorescence staining only was seen in one case with plasmocytoma. Further examination of this case and additional Romanowsky staining could demonstrate typical plasma cell morphology.

Of 20 samples obtained from patients with early stages of breast carcinoma, breast tissue-associated antigen was detected in 12 samples and DNA-synthesising tumor cells were seen in 50% of these positive cells.

Of 20 samples with known, radiologically verified metastases, the same percentage of mammary cells and of DNA-synthesising tumor cells was found.

Of 160 samples after surgery, 90 samples presented cells reacting with anti-breast tissue monoclonal antibodies. The same cells showed DNA incorporation with anti-BrdU monoclonal antibody in 45 of the 90 bone marrow samples.

Distribution of immunofluorescence positive cells

In 95% of the bone marrow samples with neoplastic cells, less than 0.5% of positive cells could be demonstrated. Solitary cells as well as clusters were labelled with the monoclonal antibodies. In the remaining 5% of positive samples, a higher proportion of labelled cells was seen. The majority of the labelled cells were dispersed throughout the cytocentrifuged slide.

DISCUSSION

Since 1981, it has been shown that there is usually no difference in monoclonal antibody reactivity between primary breast carcinoma and metastases (5,6,7,8). These antibodies are not specific for cancer but can react with a small percentage of benign lesions (8) or normal epithelial cells (9).

In the present study, however, breast tissue was demonstrated in the bone marrow. Hematopoietic cells were unreactive with anti-breast tissue antibodies, although non-specific staining could be seen in plasma cells. However, the morphology of plasma cells in phase contrast and the diffuse and weak fluorescence of these cells allowed relatively easy identification.

A few cells reactive with anti-breast tissue monoclonal antibodies have thus been found in

TABLE 2. Immunocytologic labelling reactions of bone marrow isolated cells. Percentage of patients with breast tissue-associated antigen (BTAA) and with DNA-synthetising tumor cells (DSTC)

Clinical data	No. of BTAA positive samples	No. of DSTC positive samples
Controls (n = 16)	+ (plasmocytoma)	NT*
Breast carcinoma	12/20	6/12
Breast cancer early stage (n = 20)	90/160	45/90
Patients after surgery (n = 160)	13/20	6/13
Known metastases (n = 20)		

* NT: not tested.

60% of all samples studied. A simultaneous study of DNA synthesis revealed the presence of 'proliferative' tumor cells in 50% of these cases.

The implications of these findings are not known. In a very small percentage of patients, macrometastases were detected in the weeks following. In most of the studied cases, the follow-up period does not exceed 6 months after our test and no conclusion can be drawn concerning the prognosis of patients with and without micrometastasis and the significance of proliferative mammary cells in the bone marrow in these patients with 'minimal residual disease'. Repeated immunofluorescence studies and statistical data are necessary to correlate immunologic and clinical data.

REFERENCES

1. GOSH A. K., ERBER W. N., HATTON C. S. R., O'CONNOR N. T. J., FALINI B., OSBORN M. and MASON D. Y.: Detection of metastases tumor cells in routine bone marrow smears by immuno-alkaline phosphatase labelling with monoclonal antibodies. Br. J. Haemat. 61, 21-30, 1985.
2. MUNRO-NEVILLE A., FOSTER C., REDDING H. and COOMBES R. C.: Monoclonal antibodies as probes of human breast disorders. Ann. NY Acad. Sci. 417, 251-261, 1983.
3. GRATZNER H. F.: Monoclonal antibody to 5-bromo and 5-iododeoxyuridine. A new reagent for detection of DNA replication. Science 218, 474-475, 1982.
4. VALNES K. and BRANDTZAEG P.: Selective Inhibition of nonspecific eosinophil staining or identification of eosinophilic granulocyte by paired counterstaining in immunofluorescence studies. J. Histochem. Cytochem. 29, 595-600, 1981.
5. COLCHER D., HAND P., NUTI M. and SCHLOM J. A.: A spectrum of monoclonal antibodies reactive with human mammary tumors cells. Proc. natn. Acad. Sci. U.S.A. 78, 3199-3203, 1981.
6. FOSTER C. S., DINSDALE E. A., EDWARDS P. A. and NEVILLE A. M.: Monoclonal antibodies to the human mammary gland. II. Distribution of determinants in breast carcinomas. Virchows Arch. Path. Anat. Histol. 394, 295-305, 1982.
7. NUTI M., TERAMOTO Y. A., MARIANI-COSTANTINI R., HAND P. H., COLENER D. and SCHLOM J.: A monoclonal antibody (B27.3) defines patients of distribution of a novel tumor associated antigen in human mammary cell populations. Int. J. Cancer 29, 539-545, 1982.
8. TERAMOTO Y. A., MERIANI R., WUNDERLICH D. and SCHLOM: The immunohistochemical reactivity of a human monoclonal antibody with tissue sections of human mammary tumors. Cancer 50, 241-249, 1982.
9. ARKLIE J., TAYLOR-PAPADIMITRIOU J., BODMER W., EGAN M. and MILLIS R.: Differentiation antigens expressed by epithelial cells in the lactating breast are also detectable in breast cancers. Int. J. Cancer 28, 23-29, 1981.
10. THOMPSON C. H., JONES S. L., WHITEHEAD R. H. and MCKENZIE I. F. C.: A human breast tissue-associated antigen detected by a monoclonal antibody. J. natn. Cancer Inst. 70, 409-419, 1983.

Treatment

FRAXIPARINE®
une nouvelle dimension dans la prévention de la maladie thrombo-embolique

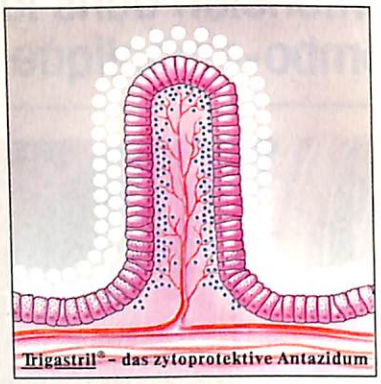
Prix Galien 1987

Sanofi-Labaz s.a. - Avenue De Béjar 1 - 1120 Bruxelles

sanofi LABAZ

Une contribution majeure dans la thrombose

Trigastril®



das zytoprotektive Antazidum regeneriert und stabilisiert die Mukosa-Barriere bei

- Reizmagen
- Gastritis
- Erosionen
- Ulzera

Trigastril® 75 Gel · Trigastril® 50 Granulat · Trigastril® Tabletten · **Zusammensetzung:** Trigastril® 75 Gel: 10 ml (≙ 1 Beutel bzw. 1 Einzeldosis ≙ 11,87 g) enthalten: Aluminiumhydroxidgel 7752 mg (≙ 969 mg Aluminiumoxid), Magnesiumhydroxid 350 mg, Calciumcarbonat 300 mg. Trigastril® 50 Granulat: 1 Beutel (≙ 3,1 g Granulat) enthält: Aluminiumhydroxidgel 1214,5 mg (≙ 646 mg Aluminiumoxid), Magnesiumhydroxid 233 mg, Calciumcarbonat 200 mg. Trigastril® Tabletten: 1 Tablette enthält: Aluminiumhydroxidgel 607 mg (≙ 323 mg Aluminiumoxid), Magnesiumhydroxid 117 mg, Calciumcarbonat 100 mg. **Anwendungsgebiete:** Magenschleimhautentzündungen, Magen- und Zwölffingerdarmgeschwüre (Ulcus ventriculi et duodeni) sowie Entzündungen der Speiseröhre durch Rückfluß von Mageninhalt (Refluxösophagitis) vor allem im Zusammenhang mit Beschwerden wie Völlegefühl, Sodbrennen, saurem Aufstoßen und Schmerzen; Magenbeschwerden durch Diätfehler und Medikamente. Trigastril® 75 Gel: Streßulkusprophylaxe. **Gegenanzeigen und Anwendungsbeschränkungen:** Hypercalcämie, Hypermagnesämie. **Hinweis:** Bei schweren Nierenfunktionsstörungen ist die Anwendung von täglich mehr als 12 Einzeldosen (≙ 120 ml) Trigastril® 75 Gel, 18 Beuteln Trigastril® Granulat bzw. 4,2 mg Magnesiumhydroxid (entsprechend 36 Trigastril® Tabletten) zu vermeiden. **Nebenwirkungen:** Trigastril® kann den pH-Wert des Urins beeinflussen, was insbesondere bei Patienten mit Nierensteinen (Calciumphosphatsteinen) wichtig ist. Bei Patienten mit eingeschränkter Nierenfunktion kann es zu einer Erhöhung des Aluminium- und Magnesiumspiegels im Serum kommen. Eine hohe Dosierung über einen längeren Zeitraum kann zu einer Störung des Säure-Basen-Haushaltes (Alkalisierung) führen. Trigastril® 75 Gel und Trigastril® 50 Granulat: Änderung der Stuhlbeschaffenheit und der Stuhlfrequenz sowie Verstopfung sind insbesondere bei hoher Dosierung möglich. Trigastril® 75 Gel enthält p-Hydroxibenzoesäureester als Konservierungsstoffe. Bei Personen, die gegen diese Stoffe empfindlich sind, können allergische Reaktionen ausgelöst werden. **Wechselwirkungen mit anderen Mitteln:** Trigastril® sollte nicht zeitgleich mit anderen Arzneimitteln (z. B. Tetracyclinen, Digoxin, Desoxycholsäurederivaten, eisenhaltigen Präparaten, Cimetidinderivaten) eingenommen werden, da deren Resorption beeinflußt werden kann. Deshalb sollten andere Arzneimittel in ein- bis zweistündigem Abstand zu Trigastril® eingenommen werden.

Darreichungsformen und Packungsgrößen: Trigastril® 75 Gel: Packung mit 20 Beuteln Gel DM 18,25, Packung mit 50 Beuteln Gel DM 39,90, Packung mit 200 ml Gel DM 18,25, Packung mit 2 x 200 ml Gel DM 31,75. Trigastril® 50 Granulat: Packung mit 20 Beuteln Granulat DM 15,95, Packung mit 50 Beuteln Granulat DM 34,70. Trigastril® Tabletten: Packung mit 20 Tabletten DM 8,70, Packung mit 50 Tabletten DM 19,60, Packung mit 100 Tabletten DM 34,25, Anstaltspackungen.
Stand: Februar 1987

Trigastril®

HEUMANN PHARMA GMBH & CO · NÜRNBERG

HEUMANN PHARMA

Adjuvant Chemotherapy and the Kinetic Refractoriness of Minimal Residual Tumors

P. Reizenstein and G. Mathé

Division of Hematology, Karolinska Hospital, S-10401 Stockholm, Sweden

Institut de Cancérologie et d'Immunogénétique (Université Paris-Sud, CNRS VA 04-1163), Hôpital Paul-Brousse, 94800-Villejuif, France

Abstract

If Skipper's exponential growth and 'log-kill' hypothesis is replaced by one assuming an S-shaped growth curve and a growth inhibition proportional to the product of the growth fraction and the tumor volume, little growth inhibition can be achieved in minimal tumors. This 'kinetic refractoriness' may explain why minimal residual tumors cannot be eradicated by adjuvant chemotherapy.

INTRODUCTION

At the present time, adjuvant or maintenance chemotherapy appears to be unable to prevent relapses in the majority of patients with tumors. In postmenopausal and even premenopausal breast cancer, surgically removed colorectal carcinoma, small cell lung cancer, low grade malignancy and possibly also high grade malignancy Hodgkin and non-Hodgkin lymphoma, malignant melanoma, myeloma and acute non-lymphatic leukemia, the effect of adjuvant or non-intensive maintenance chemotherapy is at least controversial (1,2).

REMISSION INDUCTION

It is true that chemotherapy has little effect in many common solid tumors (3), but there are approximately 11 relatively rare tumors where a majority of the patients can be shown to be long term survivors or to be cured. In both adult patients and children this is true for germ cell tumors and in children for acute lymphatic leukemia. Good effects can also be obtained in some lymphomas. Most of these patients receive at least some consolidation, intensification or maintenance treatment, but whether the cure is due to this treatment or to the original induction therapy is not known.

GROWTH RATE AND CELL KILL FUNCTION

For exponentially growing experimental tumors, such as the L1210 leukemia, Harold Skipper's 'log-kill' hypothesis is valid (4). For every dose level of a cytostatic drug, a constant percentage of tumor cells is killed.

For human tumors, on the other hand, it has been suggested that the exponential growth theory is not applicable, since, together with the 'log-kill' theory, this would imply that both the growth rate and the treatment response would be greater for large than for small tumors (5). This is contrary to clinical experience.

Norton (5) has therefore suggested an S-shaped so-called 'Gompertzian' growth curve with a late lag-phase, which of course agrees with the empirical finding of contact-inhibition, decreased vascularisation and other reasons for decreased growth rates for large tumors.

If Skipper's 'log-kill' hypothesis is applied to the Gompertzian growth curve, however, this would imply that the largest tumors with a Gompertzian growth curve would be more chemotherapy sensitive than similar smaller tumors, and suboptimally treated tumors should grow only until the plateau is reached where the chemotherapy dose balances the tumor volume (5). This also is not borne out by clinical experience. Norton therefore suggests replacing the 'log-kill' hypothesis with one where the growth inhibition is proportional to the growth rate or to the growth fraction multiplied by the tumor volume in the untreated tumor. Support for this suggestion has been found in some in vitro studies of cytostatic concentration and the cell kill (6), in a number of rat and mouse tumors and in the clinical situation, where a suboptimally treated tumor is, after all, slowly reaching its maximal size.

WHY IS IT DIFFICULT TO ERADICATE MINIMAL RESIDUAL TUMORS?

Usually small tumors initially have a rapid growth rate and thus they may have a reasonably large product of growth rate and tumor volume and therefore acceptable chemotherapy sensitivity.

However, there is a kinetic 'refractoriness' in small tumors even without any enzyme induction, cell membrane changes or tumor progression. This is true both if the tumor follows an exponential and if it follows a Gompertzian or any other S-shaped growth curve, since the growth inhibition in all these cases is small if the tumor is small.

This kinetic refractoriness is quite distinct from refractoriness developing during continuing chemotherapy. Ninety per cent of myeloma patients who relapse despite continuing chemotherapy do not respond to reapplication of the original treatment. In these patients, the minimal residual tumor has acquired biochemical refractoriness, which probably potentiates the effect of kinetic refractoriness.

Residual small tumors, on the other hand, may have a relatively low chemotherapy response to a given dose level, since the product of growth fraction and tumor volume is small, particularly if the growth fraction is reduced because of tumor progression.

REFERENCES

1. PLAGNE R.: Breast tumors: a review of adjuvant chemotherapy trials. Drugs Exp. clin. Res. XII, 135-142, 1986.
2. ÖSBY E. and REIZENSTEIN P.: Clinical trials of myeloma treatment: a review. Drugs Exp. clin. Res. XII, 113-118, 1986.
3. GILBERT J. M.: Trials of adjuvant chemotherapy in colorectal cancer. Drugs Exp. clin. Res. XII, 201-209, 1986.
4. SKIPPER H. E., SCHABEL F. M. Jr and WILCOX W. S.: Experimental evaluation of potential anticancer agents. XIII. On the criteria and kinetics associated with 'curability' of experimental leukemia. Cancer Chemother. Rep. 35, 1-11, 1964.
5. NORTON L. and SIMON R.: Tumor size, sensitivity to therapy, and design of treatment schedules. Cancer Treat. Rep. 61 (7), 1977.
6. STOUT S. A., RILEY C. M. and DERENDORF H.: In vitro pharmacokinetics and pharmacodynamics of melphalan. Abstract no. 327. Transactions of Biennical Conference on Chemotherapy of Infectious Diseases and Malignancies, 26–29 April, 1987, Munich, West Germany.

Can Neo-adjuvant Chemotherapy Prevent Residual Tumors?

C. Bourut, E. Chenu and G. Mathé

Abstract

MA 16/C is a spontaneous mouse mammary adenocarcinoma. It is hormone-dependent and was injected s.c. into C3H/He female mice on day 0. Tumors were excised on day 15. Neo-adjuvant treatments were applied from day 1 to day 21 for hormonotherapy and immunotherapy and on days 1, 5 and 9 for chemotherapy. Adjuvant treatments were applied from day 21 to day 42 for hormonotherapy and immunotherapy, and on days 21, 25 and 29 for chemotherapy. Mixed (neo-adjuvant and adjuvant) treatments combined the two patterns. Chemotherapy consisted of an oxalato-platinum complex of trans-l-dach (l-OHP) at a dose of 5 mg/kg i.p. Hormonotherapy consisted of the LH-RH agonist (D-Trp6) LH-RH, at a dose of 100μg/kg i.p. Zinc gluconate (6mg/kg per os) and bestatin (6mg/kg per os) were administered as immunoregulators. Under present experimental conditions, surgery alone did not increase the life span. Both neo-adjuvant and adjuvant chemotherapy and neo-adjuvant hormonotherapy, however, when added to surgery, increased survival significantly ($p<0.02$-$p<0.03$).

INTRODUCTION

In experimental chloromas (1) and Lewis lung tumors (2) preoperative or 'neo-adjuvant' chemotherapy led to more cures than postoperative treatment. Distant metastases of human breast cancer in stages 1 and 2 have been prevented by cyclophosphamide from the day of surgery (3,4). In one study, neo-adjuvant chemotherapy plus radiotherapy even replaced surgery with 7.3% relapses after 17 months (5). In inflammatory breast cancer, the effects of chemotherapy are, of course, well known (5,6).

The present purpose was, in an experimental system, to see whether neo-adjuvant and/or adjuvant chemotherapy, hormonotherapy or immunotherapy can prevent residual tumors after surgical excision.

Institut de Cancérologie et d'Immunogénétique (Université Paris-Sud, CNRS UA 04-1163), Hôpital Paul-Brousse, 94800-Villejuif, France

MATERIALS AND METHODS

Ten groups of 16 C3H/He female mice with subcutaneous implants of carcinoma on day 0 were excised on day 15. In addition, two groups, CT, were given neo-adjuvant chemotherapy days 1, 5 and 9 (NACT) or adjuvant CT days 21, 25 and 29 (ACT) with an oxaleto-platinum complex of trans-l-dach (1-OHP, 5mg/kg body weight intraperitoneally, i.p.). Another two groups, IT, were given neo-adjuvant, T-cell immunoregulation treatment (NAIT) with zinc gluconate (6mg/kg orally, daily) and bestatin (6mg/kg, every second day, orally) on days 1–21 or adjuvant IT (AIT) on days 21–42. The last two groups, HT, were given neo-adjuvant hormonotherapy (NAHT) with the LH-RH agonist D-Trp6-LH-RH (100μg/kg i.p.) on days 1–21, or adjuvant HT (AHT) on days 21–42. The end-point was mouse survival.

RESULTS

Surgery alone

None of the mice survived 60 days. Nor did any of the untreated control mice survive. Survival was not significantly longer than for untreated mice.

Adjuvant CT

Mice given neo-adjuvant CT without surgery did not survive significantly longer than those

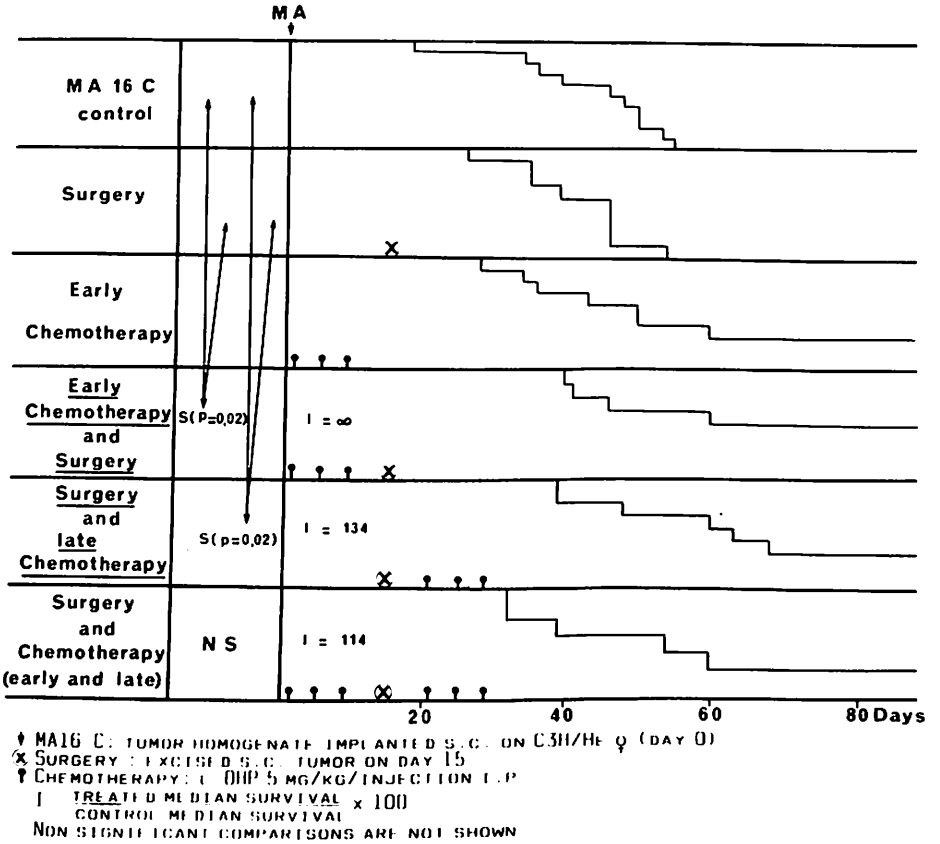
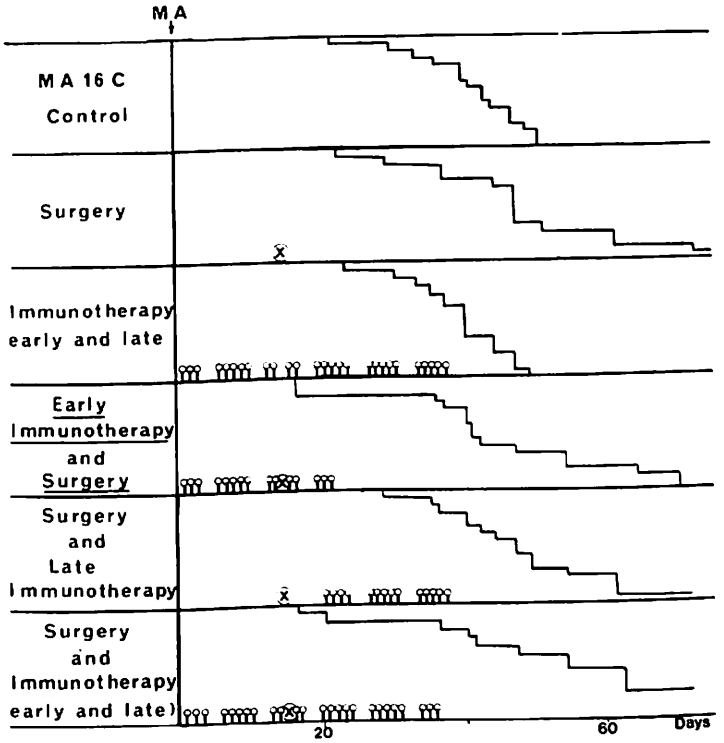


Fig. 1. Effect of surgery with or without chemotherapy on mammary carcinoma.

TABLE 1. Percent cured animals after CT, HT, IT and surgery alone

		Surgery with treatment		
	Treatment alone	Early	Late	Early + late
I-OHP	30	50	33	28
D-Trp6-LH-RH	0	33	40	37
Zn gluconate + bestatine	0	0	6	21
Surgery	0			

Surgery with or without chemotherapy, hormonotherapy or immunotherapy on mammary carcinoma (MA 16-C). Results are expressed as percentage of lifespan.



MA: MA16-C TUMOR HOMOGENATE IMPLANTED S C ON C3H/HE O (DAY 0)
EXCISED S.C. TUMOR ON DAY 15
ZN GLUCONATE 6 MG/KG EVERY DAY + BESTATIN 6 MG/KG EVERY TWO DAY

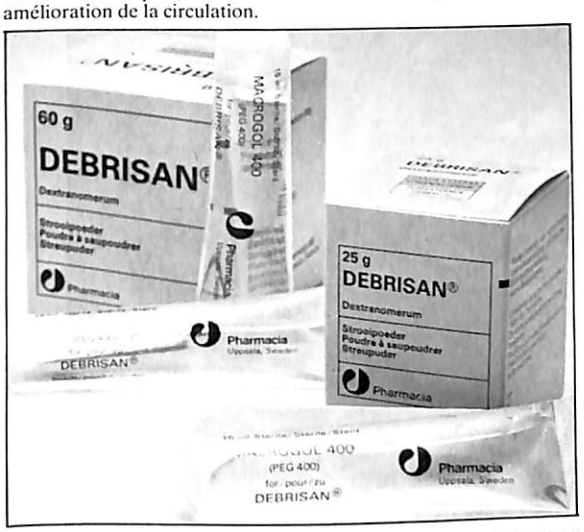
Fig. 2. Effect of surgery with or without immunotherapy on mammary carcinoma.

DEBRISAN® · NOVASORB®

détersion efficace des plaies JAUNES

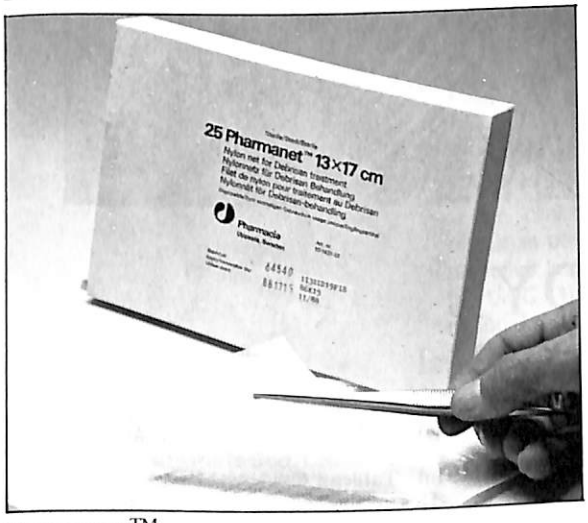
Debrisan® poudre + Macrogol 400.
Pour pâte à préparer.

Nettoyage mécanique rapide. Eloignement loin de la surface de la plaie de TOUTES les bactéries. Les matières nutritives restent en contact avec la plaie. Diminution de l'œdème et, par conséquent, amélioration de la circulation.



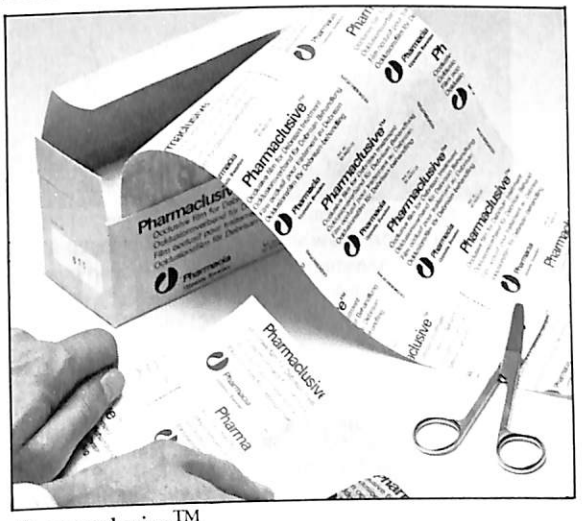
Novasorb®
Pâte prête à l'emploi, dose unique.

Pratique, hygiénique, économique. Facile à l'emploi en vue d'un traitement ambulatoire. Caractéristiques identiques à celles de la pâte Debrisan®.



Pharmanet™
Tulle stérile à placer sur la plaie avant la pâte.

Facilite l'enlèvement de la pâte détersive. N'adhère pas à la plaie. Permet un changement rapide du pansement (en combinaison avec Phamaclusive™).



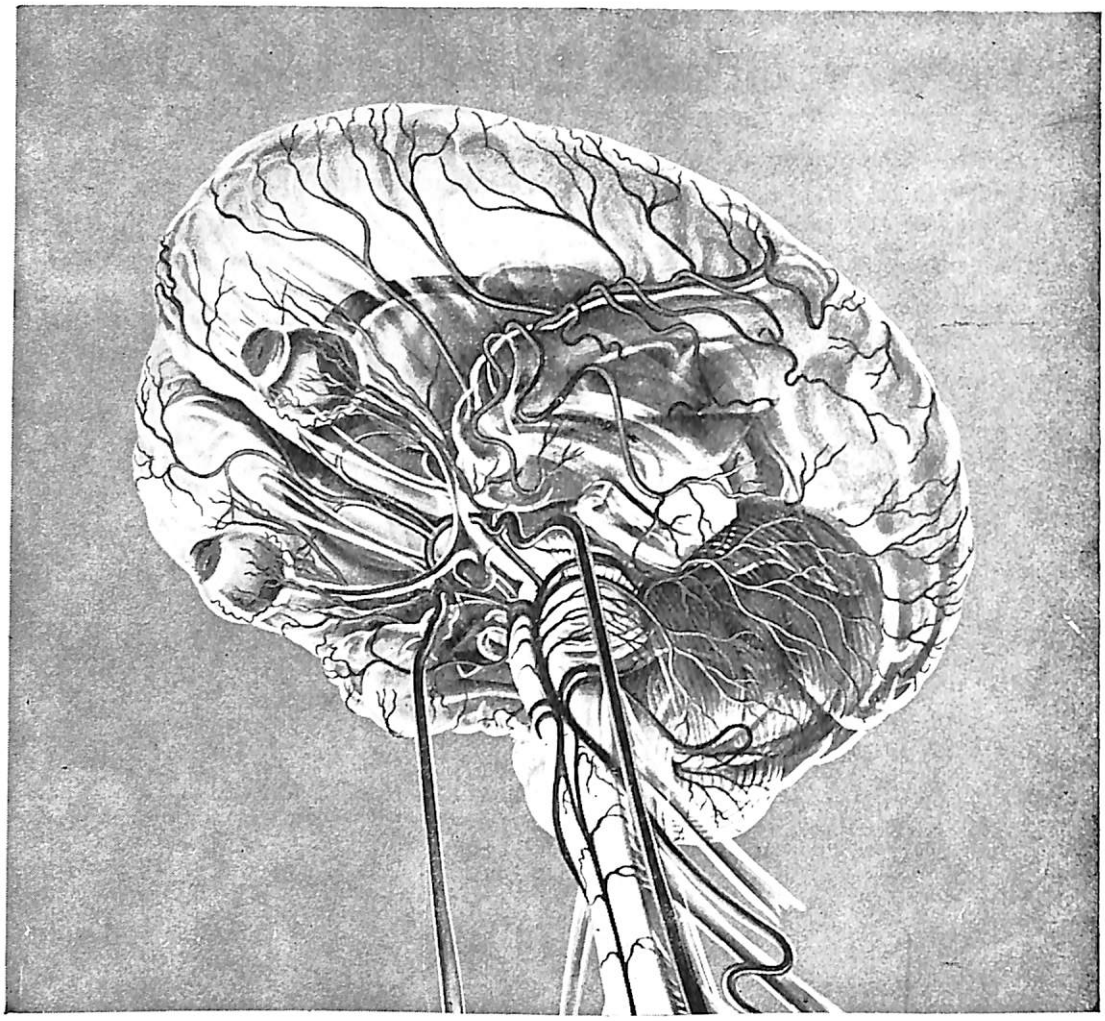
Pharmaclusive™
Pansement adhésif semi-occlusif.

Economique : utilisation plus efficace de la pâte détersive ; rend l'utilisation d'autres pansements superflue. Maintient la pâte soigneusement en place. Semi-perméable : maintient la plaie humide et laisse la peau respirer. Facilite la cicatrisation et empêche le développement des bactéries anaérobies. Facile à appliquer et à enlever.

Pour de plus amples informations, contacter Pharmacia,
nous nous ferons le plaisir de vous faire une démonstration.

Pharmacia

Rue de la Fusée 62,b 2
1130 Bruxelles
Tél. 02/242 46 60



ISKÉDYL

Vaso-régulateur cérébral

Iskédyl injectable : 3 à 6 amp./jour. N.B. Ne pas mélanger Iskédyl avec les solutés alcalins. Raubasine base : 6,25 mg, Dihydroergocristine : 0,3125 mg, excipient q.s.p. 1 amp. de 2,5 ml. Boîte de 6 ampoules de 2,5 ml - Tableau C - Visa NL 7930.
Iskédyl gouttes : 90 à 120 gouttes/jour en 3 prises. Raubasine base : 0,800 g, Dihydroergocristine (méthane sulfonate) : 0,100 g, excipient q.s.p. 100 ml de solution.
Flacon de 30 ml - Tableau C - A.M.M. 305.425.5 .
Indications : « Des vertiges aux comas vasculaires » ;
- troubles liés à l'insuffisance circulatoire cérébrale ;
- déficits sensitivo-moteurs.

Laboratoires Pierre Fabre Fimex - 125, rue de la Faisanderie, 75116 Paris
Distributeur pour le Grand Duché du Luxembourg : Prophac-Luxembourg. Tél. 48.24.82.

Délivrance sur prescription médicale
PROPHAC - Howald · 5, Rangwé · L-2412 Howald · Téléphone 48 24 82

Monitoring and Treatment of Minimal Residual Cancer of the Prostate

G. Mathé, A. V. Schally, A. M. Comaru-Schally, R. Y. Mauvernay, M. L. Vovan, D. Machover, J. L. Misset, B. Court, P. Bouchard, J. Duchier, P. Morin, R. Kelling, P. Kerbrat, E. Achille, J. C. Tronc, J. P. Fendler, E. Papo, R. Metz and G. Prevot

Service des Maladies Sanguines et Tumorales & ICIG (Université Paris-Sud, CNRS UA 04-1163), Hôpital Paul-Brousse, 94800-Villejuif, France, and Veterans Administration Medical Center and Tulane University School of Medicine, New Orleans, Louisiana, U.S.A.

Abstract

In manifest prostatic carcinoma, partial and complete remissions are obtained in 14–44% of patients as judged by different sets of criteria, but in up to 61% as judged by a decrease in prostatic acid phosphatase. Moreover, this decrease is poorly correlated to that of prostatic size. Prostatic acid phosphatase is therefore considered to be a relatively non-specific tumor marker.

A complete remission, i.e. a stage of minimal residual disease, is obtained in about 25% of the patients. Continued endocrine treatment involves the risk of a flare-up of the disease, which is probably small. Additionally, in minimal residual disease, prolonged maintenance treatment requires minimization of side effects. D-Trp-6-LH-RH appears to lead to less gynecomastia and thromboembolism than some other forms of adjuvant therapy.

RESPONSE TO TREATMENT OF CLINICALLY MANIFEST TUMORS

For clinically manifest prostatic adenocarcinoma, the response parameters used in the early 1940s were not quite objective. Improvements have therefore been recommended by the UICC (1) and further improvements by the WHO and the national prostatic cancer program (2). According to these different criteria, partial and complete remissions are seen after different forms of endocrine manipulation in 14% (3) to 50% (15) of patients (2–10).

A reduction of prostatic acid phosphatase levels is one of the most sensitive generally recognized parameters and has shown more frequent responses than any other criterion (4). The normal value of prostatic acid phosphatase is defined as being under 3.2 ng/ml in the present study. In addition to the 50% of patients whose acid phosphatase is normalized, there are 11% in which it was reduced by more than half. However, it is possible

that lipid-associated sialic acid (LASA) is even more sensitive (Sectior. 1, this volume).

The LH-RH analog, D-Trp-6-LH-RH (Fig. 1) has been shown to cause desensitization of the pituitary 'down-regulation' of receptors and suppression of Leydig cell function in animals and in man (11,12). Administration of D-Trp-6-LH-RH suppressed plasma LH and testosterone levels substantially (Figs 2 and 3). This drug can induce a regression of more than 50% in tumor volume in at least 37% of patients after 3 months of therapy (13–15). The reduction of tumor volume was evaluated by rectal examination of the prostate and transabdominal ultrasonography (the results of these are in good agreement, Fig. 4) (16,17), and by computerized tomography. Only a small reduction (12.5%) in the size of bone lesions, determined by isotope scanning, was noted.

In addition, an early improvement was seen in symptoms of urinary outflow obstruction (prostatism, Fig. 5). After 90 days, 52 patients showed complete relief of prostatism and 21 had only mild signs and symptoms. Similarly, a

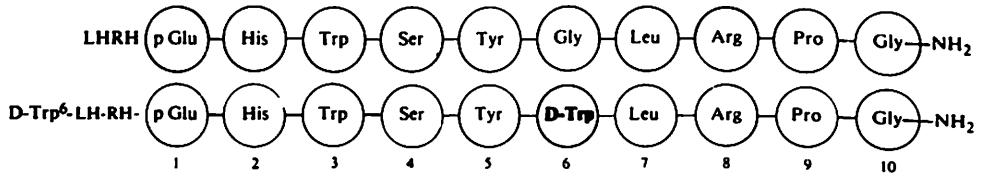


Fig. 1. Structure of D-Trp-6-LH-RH.

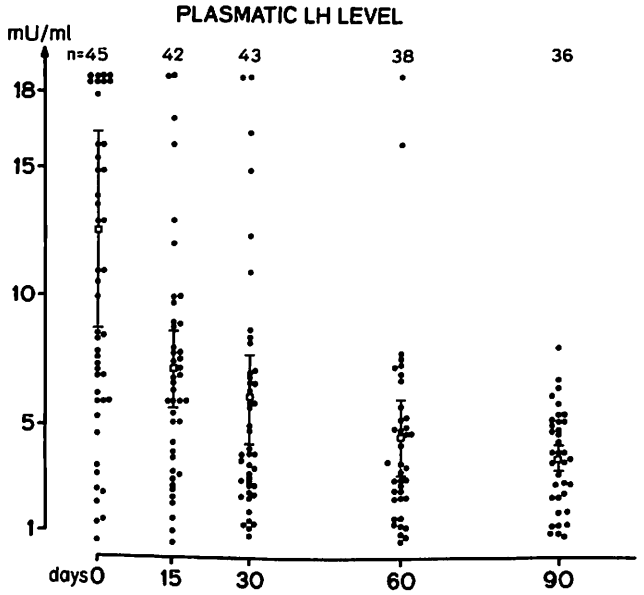


Fig. 2. Plasma LH level before the first injection of D-Trp-6-LH-RH and after 15, 30, 60 and 90 days.

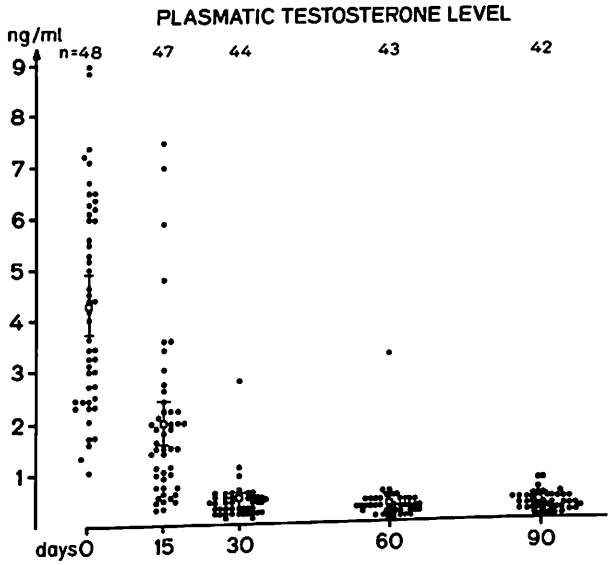


Fig. 3. Plasma testosterone level before the first injection of D-Trp-6-LH-RH and after 15, 30, 60 and 90 days.

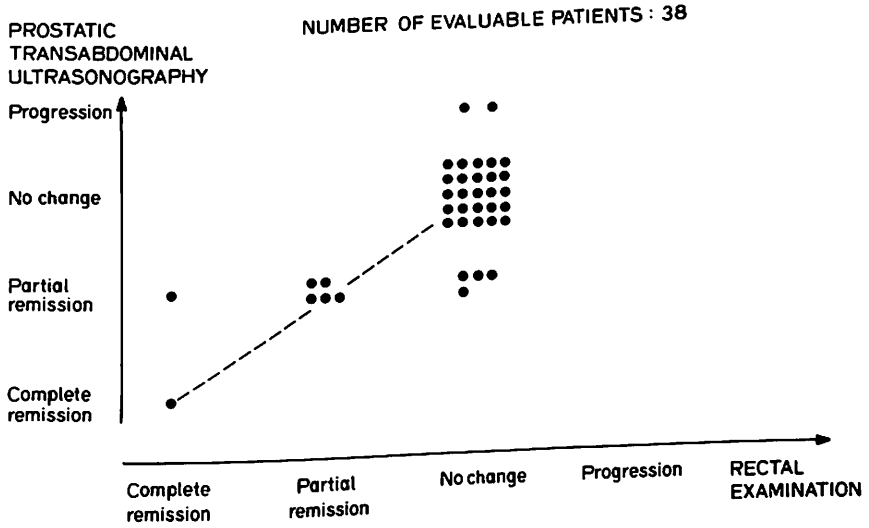


Fig. 4. Correlation between prostatic volume as evaluated by rectal and ultrasonographic examinations.

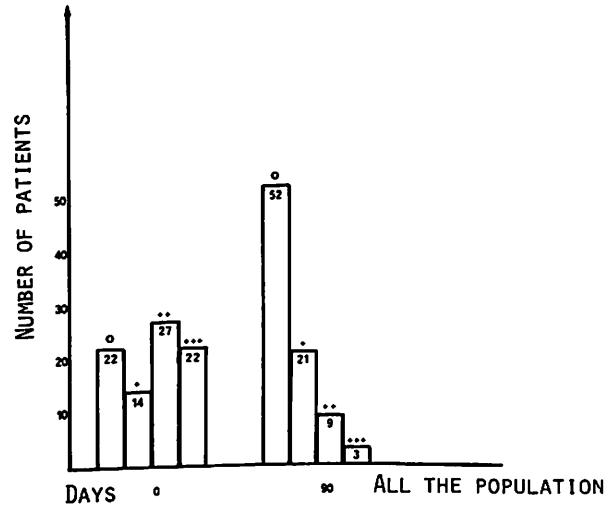


Fig. 5. Prostatism: evaluation at 3 months of therapy. Intensity 0 to +++.

decrease in bone pain was seen after a few days or a week of therapy. After 90 days, 70 patients were free of bone pain and an additional 6 had only mild pain (Fig. 6).

When the response is based on the decrease in prostatic acid phosphatase levels, the results are not correlated with the estimation of the prostate size (17) (Fig. 7). On the basis of prostatic acid phosphatase levels, the total incidence of regression was 66.7%, of which 41% was complete and 25% only partial, a result which shows a positive bias. The reason for the overestimation of response with

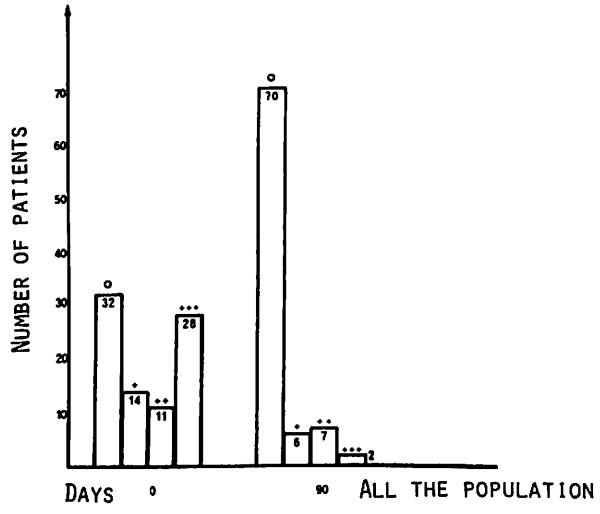


Fig. 6. Bone pain: evaluation at 3 months of therapy. Intensity 0 to +++: 0 none, + mild, ++ moderate, +++severe.

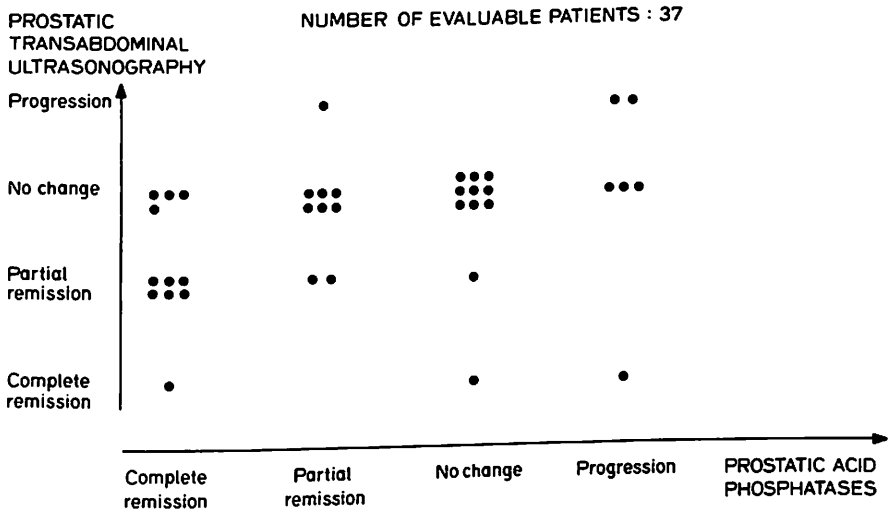


Fig. 7. Absence of correlation between transabdominal ultrasonography and prostatic acid phosphatase levels.

acid phosphatase may be that this test measures only the differentiated cell volume.

In conclusion, the best parameter to establish the response of manifest prostatic carcinoma is the reduction in size of the prostate estimated by transabdominal ultrasonography or rectal examination (17). The incidence of regression based on these parameters is smaller than that based on prostatic acid phosphatase levels (Table 1), and there is no correlation between them (Fig. 7).

POSSIBILITIES FOR TREATMENT OF MINIMAL RESIDUAL PROSTATIC CANCER

A complete remission, i.e. a stage of minimal residual disease can be achieved in between 1/3 and 1/4 of the patients (Tables 2 and 3).

Continued treatment with D-Trp-6-LH-RH in the minimal residual stage of prostatic cancer has been reported to lead to a flare-up of the disease (18). This has not been observed, however, in any of our patients subjected to

TABLE 1. Evaluation of prostatic acid phosphatases after 3 months of therapy with D-TRP-6-LH-RH in 28 patients with prostate cancer

	Normalization	$R \geqslant 50\%$*	$R < 50\%$†	No change	Progression
No. of patients	14	3	1	8	2
Response rate (%)	50	11	3.5	28.5	7
	61				

* Regression $\geqslant$ 50% compared with the initial value.
† Regression $<$ 50% compared with the initial value.

TABLE 2. Patients with prostate cancer: stages of disease and stage D localization; previous therapy

	No. of patients
Stage B	8
Stage C	9
Stage D	
Bone metastases only	48
Bone + lung metastases	5
Bone + lymph node metastases	5
Bone + lymph node + lung metastases	1
Bone + bone marrow metastases	2
Lymph node metastases only	3
Total	64
Previously untreated	24
Previous hormonal therapy	40
Previous surgery	11
Previous chemotherapy	0
Previous radiotherapy	6

hormonal treatment for 3 month periods. If treatment of minimal residual prostatic cancer is considered, D-Trp-6-LH-RH is more effective than estrogens (2) which suppress testosterone secretion by inhibiting gonodadotropin release (12). A major advantage of D-Trp-6-LH-RH over estrogens is that it does not have any secondary metabolic effects. Estrogens raise plasma prolactin, which increase androgen transport into the cells.

Prolonged maintenance treatment of nonsymptomatic minimal residual disease is difficult if side effects are pronounced.

Table 4 lists the comparative side effects of the different endocrine treatments of prostatic carcinoma, according to Geller and Albert (8). It is difficult to compare the incidence of side-effects of D-Trp-6-LH-RH with other hormonal treatments of prostatic carcinoma, because of dose differences. Other investigators registered 38% adverse cardiovascular effects with DES, 14% with CPA and 20% with MPA (7). It is possible that equally beneficial results might have been obtained with lower doses of these hormones, with fewer side-effects. In addition, the duration of treatment varied. It should be mentioned that painful gynecomastia appears in 40% of patients treated with DES (6), but in only 6% of those receiving CPA and MPA (7). This complication was not observed in a single patient in our study.

The side-effects and mechanisms of action discussed above must be considered in reaching a decision on the indications for treatment with D-Trp-6-LH-RH, given alone or in combination. Because of the two cases of apparent disease flare-up at the onset of the treatment with D-Trp-6-LH-RH (18), an initial combination with an antiandrogen was suggested. Labrie et al. (19) claimed a high incidence of beneficial results obtained by the combination of buserelin with the antiandrogens, anadron or flutamide. Unfortunately, an accurate oncologic evaluation of their results is difficult (20). Moreover, the authors (19) mentioned the regression of pain (which is a subjective manifestation), in nine out of ten patients and a fall in serum acid phosphatases (a test which may not be valid) in three out of four patients, as well as a reduction in alkaline phosphatases in five out of six patients. However, neither ultrasonographic changes, nor changes of LASA levels were reported (19). It is not known at present whether these combinations have significant advantages over the LH-RH agonists alone and whether such a possible advantage would be nullified by toxic side-effects of the antiandrogens, especially on the liver.

An important point in selecting hormonal therapy for prostate cancer is the finding that D-Trp-6-LH-RH is more effective than castration (Table 4), at least over a short time period. The psychological and social complications of castration are sometimes severe. Impotence is a complication of both types of treatment, but it is permanent after castration and reversible after LH-RH agonists.

TABLE 3. Prostatic volume at rectal examination and transabdominal ultrasonography after 3 months of treatment with D-TRP-6-LH-RH

	Complete remission —normalization	Partial remission objective, $R \geqslant 50\%$†	Minor remission objective, $R < 50\%$‡ with major life quality improvement	No change	Progression
No. of patients	9	6	10	9	0
Response rate	26.4%	17.6%	29.4%	26.4%	
		44%			
			73.5%		

No. of evaluable patients = 34.
* In which the ultrasonography image was initially abnormal.
† Regression ⩾ 50%: with three-dimensional evaluation.
‡ Regression < 50%, proven or not proven with three-dimensional evaluation.

TABLE 4. Comparative side effects of various therapies for prostate carcinoma

D-Trp-6-LH-RH		Castration	DES	Megestrol plus low dose of DES or estradiol	Flutamide	LHRH agonist plus antiandrogen
Gynecomastia*	—	0	++++	+	++	?
Loss of libido	Yes	Yes	Yes	Yes	No	Yes
Salt retention	No	No	Yes	No	No	No
Thromboembolism	No	No	Yes	No	No	?
Convenience	Yes	No	Yes	Yes	Yes	No
Cost	?	One time cost only	Inexpensive	$60/Month	?	? High

* Intensity: 0 to ++++.

It appears that D-Trp-6-LH-RH and other agonists can advantageously replace estrogens because the agonists may be more effective in the same kind of tumors and are without the short-term complications such as gynecomastia. It seems that D-Trp-6-LH-RH, unlike estrogens (21), will not cause thromboembolic complications, but additional, careful, long-term studies will be needed to demonstate this with certainty.

One of the most pressing questions concerns the advisability of combining LH-RH agonist with an antiandrogen, the choice of the

latter and especially the optimal timing of combination therapy. As complete remissions are obtained with D-Trp-6-LH-RH alone, we think that it is more rational for patients with prostate cancer to be treated first only with an LH-RH agonist. In case of failure, or appearance of resistance, antiandrogens can be tried. It is not advantageous or rational to use a therapeutically inert drug in a combination. Other hormonal treatments cannot be expected to work when a LH-RH agonist and an antiandrogen are not effective. Unresponsiveness to these agents would imply that the tumor is hormone-insensitive, which is an indication for chemotherapy.

Instead of combining both hormonal and cytostatic treatments at random, we have chosen our present approach on the basis of some theoretical considerations and findings. It is known that in hormone-dependent tumors there are cell clones which do not carry receptors for hormones or in which the receptors are not activated, but these clones are sensitive to cytostatics. We have shown in castrated animals (22) that hormonal treatment which stimulates cell division recruits the cells into the cycle, partially synchronizes the cycle phase of cell growth and significantly enhances their sensitivity to cytostatics. Consequently, we decided to start the combined treatment with D-Trp-6-LH-RH and apply chemotherapy 10 hours later at the time of the transitory peak of androgen. On the basis of CR and PR, the most efficacious cytostatic agents on prostate carcinoma are platinum complexes (31.6%), anthracyclines (25%), 5-fluorouracil (12%) (10) and bleomycin (23,24).

Thus, we are currently using in prostatic carcinoma patients D-Trp-6-LH-RH alone for a few hours until LH and testosterone levels increase. We then start chemotherapy combining, in cycles, 5-fluorouracil modulated by folinic acid (24), the new platinum complex 1-OHP (25,26) and a new anthracyclin, THP-adriamycin (27), which has no cardiac toxicity (28); pepleomycin is also given midway in the treatment cycles of 2–3 weeks (23). Hormonal therapy and chemotherapy are continued until maximal regression is attained.

At the stage of minimal residual tumor, a combined therapy (hormonal, immunorestorative and cell differentiating) is applied as well. The hormonal treatment consists of an intermittent application of D-Trp-6-LH-RH; the differentiating agents employed are bestatin and zinc gluconate (29). It is also known that D-Trp-6-LH-RH exerts an immunorestorative action (30). In addition, we have been able to demonstrate a significant protective effect on the bone marrow stem cells by D-Trp-6-LH-RH both in vivo and in vitro (31). The results of this combined approach will be reported after a complete evaluation is made. In a few cases, we have been tempted, facing the apparently complete tumor volume regression, to subject the patients to prostatectomy. This operation, using the technique established by Walsh (32), does not induce impotence, in contrast to radiotherapy, which is also complicated by cystitis, rectitis and iliac bone metastasis enhancement (33). It is possible that controlled studies on the effect of intermittent or alternating treatment of prostatic carcinoma in complete remission with hormone–cytostatic combinations are indicated, perhaps even after prostatectomy, in an effort to study the effect of such treatment on remission, duration of survival and incidence of possible cure.

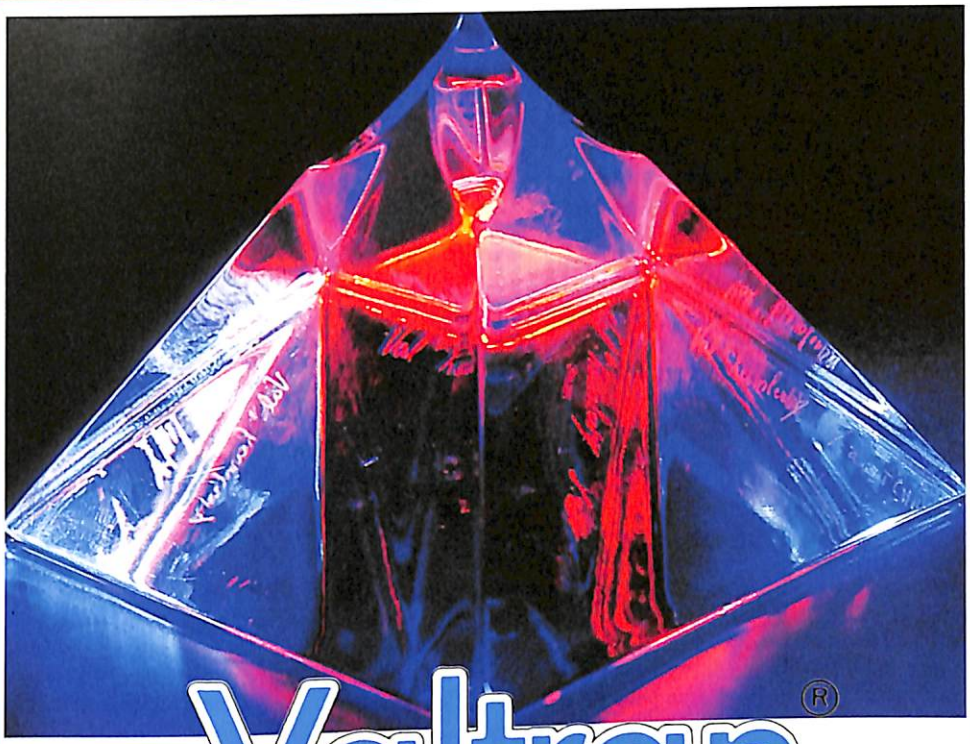
Acknowledgements

We are grateful to Dr William Locke, Ochsner Clinic, and Dr Ray Randal, Mayo Clinic, for valuable suggestions and generous advice in the preparation of this manuscript.

This study was supported in part by Debiopharm, Lausanne, Switzerland.

REFERENCES

1. COFFEY D. S. and ISAACS J. T.: Prostatic Cancer, UICC Techn. Rep. Series 48, 229-241, 1979.
2. HORTON J.: Cancer of the prostate. Methods of evaluating new therapeutic modalities: recent results of the NPCP. Prostate Cancer. UICC Techn. Rep. Series 48, 264-289, 1979.



Valtran®

Tilidine + naloxone

l'analgésique à la mesure de la douleur

10 à 40 gouttes par prise,
3 à 4 fois par jour

Voir notice en fin d'ouvrage.

PARKE-DAVIS, division of Warner-Lambert, Belgium

Valtran®

Tilidine + naloxone.

Description : VALTRAN est composé de tilidine et de naloxone. La tilidine est une substance originale (C_{17} H_{23} NO_2 HCl. 1/2 H_2O), chimiquement apparentée au groupe des morphiniques. La naloxone est un antagoniste pur des analgésiques de type morphinique. VALTRAN est destiné à l'administration orale. Aux doses thérapeutiques recommandées, la naloxone est entièrement éliminée lors de son premier passage par le foie (first pass effect) et de ce fait n'antagonise nullement les effets de la tilidine. Cependant, lors de l'ingestion de doses supra-thérapeutiques ou en cas d'abus, une partie de la naloxone ingérée ne sera pas éliminée par le foie et antagonisera les effets de la tilidine. La possibilité d'abus du VALTRAN paraît très réduite, on ne peut cependant pas la considérer comme inexistante. L'avantage majeur du VALTRAN réside dans le fait que son action analgésique est rapide et puissante après administration orale; cette caractéristique se retrouve rarement chez les autres analgésiques puissants. L'action analgésique de VALTRAN débute en moyenne 10 à 20 minutes après la prise et sa durée d'action est en général de 4 à 6 heures. VALTRAN est présenté sous forme de gouttes. 20 gouttes = 50 mg de tilidine + 4 mg de naloxone. — **Indications :** Traitement symptomatique des douleurs modérées à intenses, aiguës ou chroniques d'origines diverses. — **Contre-indications :** Le VALTRAN ne sera pas administré aux malades qui ont présenté antérieurement une hypersensibilité à cette substance. — **Précautions :** Des études de reproduction pratiquées chez l'animal n'ont pas mis en évidence d'effet tératogénique ou embryotoxique; cependant la sécurité d'emploi du VALTRAN au cours de la grossesse chez la femme n'a pas été établie. Jusqu'à plus ample informé, le VALTRAN ne sera pas administré aux femmes enceintes. On évitera des traitements prolongés chez les enfants. En cas d'insuffisance rénale ou hépatique, on réduira la posologie du VALTRAN. Il est conseillé d'évaluer soigneusement l'opportunité d'administrer le VALTRAN chez un malade ayant un passé, ou suspecté d'abus de substances psychotropes. Chez des sujets toxicomanes aux opiacés, il est à noter que l'emploi abusif de VALTRAN (à des doses dépassant les doses thérapeutiques préconisées) pourra provoquer un syndrome de sevrage, ou intensifiera celui-ci s'il est déjà présent. **Effets secondaires :** Le VALTRAN est généralement bien toléré; parfois il peut apparaître des effets secondaires : vertiges, somnolence, nausées, vomissements. Ces effets secondaires sont fonction de la sensibilité individuelle du malade et de la dose administrée. Ils sont généralement plus prononcés chez les malades ambulants. De ce fait, on évitera, surtout au début du traitement, de conduire un véhicule ou de s'engager dans des activités qui exigent une concentration mentale adéquate. On sera attentif au fait que la somnolence parfois provoquée par le VALTRAN peut être renforcée par des médicaments à action déprimante sur le système nerveux central (alcool, tranquillisants, sédatifs, antihistaminiques, etc.). Vertiges et nausées furent réduits à leur minimum en limitant l'effort physique chez le malade ambulant et, en cas de nécessité, ils peuvent être aisément maîtrisés en couchant le malade. On n'a pas mis en évidence de perturbation au niveau du système hématopoïétique, des fonctions rénale et hépatique, lors d'administration prolongée de la tilidine. — **Posologie et mode d'administration :** Gouttes (à ne pas diluer). En moyenne, 10 à 20 gouttes, 4 × par jour, à avaler pures ou sur un morceau de sucre. — En cas de besoin on peut doubler les posologies journalières : il est inutile de dépasser cette dose maximale. — **Présentations :** Flacons de gouttes de 10 ml-20 ml. — **Formule :** Tilidini hydrochloridum hemihydricum (= Tilidini hydrochloridum 50 mg) - Naloxoni hydrochloridum 4 mg - Aethanolum - Acidum hydrochloridum concentratum - Aqua purificata q.s. ad 0,7225 ml = 20 gouttes.

S 1237

Il n'est pas recommandé d'administrer Valtran® à un malade suspecté d'abus ou ayant un passé de pharmacodépendance.
Les spécialités à base de tilidine tombent sous la réglementation prévue par l'A.R. du 31 décembre 1930 concernant le trafic des substances soporifiques et stupéfiantes. Toutefois, conformément à l'A.R. du 25 mars 1982, les pharmaciens peuvent délivrer Valtran® contre remise d'une ordonnance médicale ordinaire.

3. BLOCK M., BONOMI P., ANDERSON K., WOLTER J., SCHOWEL J., PESSIS D. and SLAYTON R.: Treatment of stage D of prostatic carcinoma with megestrol acetate. J. Surg. Oncol. 17, 367-378, 1981.
4. SOGANI P. C., VAGAIWALA M. R. and WHITMORE W. F. Jr.: Experience with flutamide in patients with advanced prostatic cancer without prior endocrine therapy. Cancer 54, 744-750, 1984.
5. MUSSET M., VOVAN M. L. and MATHÉ G.: Lipid bound sialic acid vs prostatic acid phosphatases as prostate cancer marker. Biomed. Pharmacother., in press.
6. STEG A. and BENOIT G.: Étude comparative de fortes doses d'oestradiol -17-β administrees par voie per-cutanee et de l'orchiectomie bilaterale dans le traitement du cancer de la prostate. Ann. Urol. 17, 286-288, 1983.
7. PAVONE-MACALUSO M. and the EORTC Urological Group: Medroxyprogesterone acecate in the treatment of prostatic cancer: preliminary results of EORTC trial 30761 comparing MPA with stilbestrol and with cyproterone acetate, in CAMPIO L., DELLA CUNA R. and TAYLOR T. W. (eds): Role of Medroxyprogesterone in Endocrine-related Tumors, Vol. II, pp. 183-190. New York, Raven Press, 1983.
8. GELLER J. and ALBERT D.: Comparison of various hormonal therapies for prostatic carcinoma. Sem. Oncol. 10, 34-40, 1983.
9. TRACHTENBERG J., HALPERN N., PONT A.: Ketoconazole: a novel and rapid treatment for advanced prostatic cancer. J. Urol. 130, 152-153, 1983.
10. PINTER J. (ed): Prosztata Rak. Budapest, Molnar Laszlo Munkaja, 1983.
11. SCHALLY A. V., REDDING T. W. and COMARU-SCHALLY A. M.: Inhibition of the growth of some hormone-dependent tumors by D-Trp-6-LH-RH., Med. Oncol. Tumor Pharmacother. 1, 109-118, 1984.
12. TOLIS G., MEHTA A., COMARU-SCHALLY A. M. and SCHALLY A. V.: Suppression of androgen production by D-tryptophan-6-luteinizing hormone-releasing hormone in man. J. clin. Invest. 68, 819-822, 1981.
13. MATHÉ G.: La D-Trp-6-LH-RH, nouveau traitement rationnel des cancers de la prostate et du sein. Premiers resultats, in Actualites Cancerologiques, Entretiens de Bichat, pp. 223-224. Paris, Expansion Scientifique Francaise, 1983.
14. MATHÉ G., SCHALLY A. V., VO VAN M. L., DOUCHIER J., MISSET J. L. and KEILING R.: Un analogue de la gonadoliberine dans le traitement des carcinomes prostatiques. Nouv. Presse Med. 13, 1443-1445, 1984.
15. MATHÉ G., VO VAN M. L., DUCHIER J., MISSET J. L., MORIN P., KEILING R., SCHWARZENBERG L., KERBRAT P., ACHILLE E., TRONC J. C., MACHOVER D., FENDLER J. P., PAPPO E., METZ R., PREVOT G., COMARU-SCHALLY A. M. and SCHALLY A. V.: An oriented phase II trial of D-Trp-6-LH-RH in patients with prostatic carcinoma. Med. Oncol. Tumor Pharmacother. 1, 119-122, 1984.
16. GEHAN E. A.: The determination of the number of patients required in a preliminary and a follow-up trial of a new therapeutic agent. J. chron. Dis. 13, 346-353, 1961.
17. MATHÉ G. and VO VAN M. L.: Echotomographic vs clinical rectal examination of local prostate cancer. Biomed. Pharmacother., in press.
18. KAHAN A., DELRIAU F., AMOR B., CHICHE B. and STEG A.: Disease flare induced by D-Trp-6-LH-RH analogue in patients with metastatic prostatic cancer. Lancet I, 971-972, 1984.
19. LABRIE F., DUPONT A., BELANGER A., CUSAN L., LACOURCIERE Y., MONFETTE G., LABERGE J. G., EDMOND J. P., FAZEKAS A. T. A., RAYNAUD J. P. and HUSSON J. M.: New hormonal therapy in prostatic carcinoma: combined treatment with an LHRH agonist and an antiandrogen. J. clin. invest. Med. 5, 267-275, 1982.

20. MILLER A. B., HOOGSTRATEN B., STAQUET M. and WINKLER A.: Reporting results of cancer treatment. Cancer 47, 207-214, 1981.
21. Veterans Administration Cooperative Urological Research Group: Treatment and survival of patients with cancer of the prostate. Surg. Gynec. Obstet. 124, 1011-1017, 1967.
22. MATHÉ G.: Enhancement of cytostatic effect by estrogens in castrated mouse mammary tumors. Biomed. Pharmacother., in press.
23. EDSMYR F., ESPOSTI P. L., ANDERSSON L., NASLUND I. and BLOMGREN H.: Clinical study on bestatin and pepleomycin in treatment of prostatic carcinoma, in CARTER S. K. and ULTMAAN J. (eds): Pepleomycin: Proc. Int. Congress Chemother., Vienna, August 28–September 2, SY 87-2, pp. 5-7, 1983.
24. MACHOVER D., SCHWARZENBERG L., GOLDSCHMIDT E., TOURANI J. M., MICHALSKI B., HAYAT M., DORVAL T., MISSET J. L., JASMIN, C., MARAL R. and MATHÉ G.: Treatment of advanced colorectal and gastric adenocarcinomas with 5-FU combined with high-dose folinic acid: a pilot study. Cancer Treat. Rep. 66, 1803-1807, 1982.
25. MATHÉ G., KIDANI K., NOJI M., BOURUT C. and CHENU E.: Antitumor activity of 1-OHP in mice. Cancer Lett. 27, 135-143, 1985.
26. MATHÉ G., KIDANI K., TRIANA K., BRIENZA S., RIBAUD P., GOLDSCHMIDT E., ECSTEIN E., DESPAX R., MUSSET M. and MATHÉ G.: A phase I trial of trans- and diamino-cyclohexane oxalato-platinum (1-OHP). Biomed. Pharmacother. 40, 372-376, 1986.
27. MATHÉ G., UMEZAWA H., OKA S., MISSET J. L., BRIENZA S., DE VASSAL F., MUSSET M., RIBAUD P. and TAPIERO H.: An oriented phase II trial of THP-adriamycin in breast carcinoma. Biomed. Pharmacother. 40, 376-379, 1976.
28. DANTCHEV D., PAINTRAND M., BOURUT C. and MATHÉ G.: Low heart and skin toxicity of a tetra-hydropyranyl derivative of adriamycin (THP-ADM) as observed by electron and light microscopy. J. Antibiot. 32, 1085-1086, 1979.
29. MATHÉ G., BLAZSEK I., CANON C., GILDELGADO M. and MISSET J. L.: From experimental to clinical attempts in immunorestoration with bestatin and zinc. Comp. Immun. Microbiol. infect. Dis. c, 241-252, 1986.
30. CUPISSOL P.: personal communication.
31. LEMAIGRE G., MARAL R., BOURUT C., CHENU E., BLAZSEK I., MAUVERNAY Y., SCHALLY A. V. and MATHÉ G.: Experimental protection by a LH-RH agonist of a bone marrow nitrosourea aplasia. Preliminary results. Cancer Lett. 25, 123-128, 1984.
32. WALSH P. C.: Quoted by GOLDSMITH, M. F. in: Modifications in prostate cancer operation preserve potency. J. Am. Med. Ass. 250, 2897-2899, 1983.
33. GOLDSTEIN I., FELDMAN M. I., DECKERS P. J., BABAYAN R. K. and KRANE K.: Radiation-associated impotence. J. Am. Med. Ass. 251, 903-910, 1984.

Adjuvant Treatment of Minimal Residual Tumors. A Comparison of Chemotherapy and Immunotherapy

G. Mathé, P. Reizenstein and M. Erlguchi

Abstract

Adjuvant chemotherapy. The frequent 6 month complete remission induction chemotherapy is not discussed here. What is under debate at present is the prolonged maintenance or adjuvant chemotherapy, which in comparative trials with 5 year follow-up does not appear to improve survival prognosis in leukemia, myeloma, non-Hodgkin lymphoma or post-menopausal breast cancer. However, it may prolong the duration of the first remission.

It is suggested that the sensitivity to chemotherapy might depend on cells being induced into the G_2 or M phases by growth growth promotor(s), such as estrogens in breast carcinoma. Their presence before the menopause could explain why this neoplasia in this condition is one of the few tumoral diseases transitorily sensitive to adjuvant chemotherapy.

Adjuvant immunotherapy is also under debate. Immuno-therapy has been reported to give a significant improvement in remission duration and/or overall survival and/or survival after relapse in several tumors and in several trials. However, for almost every trial reporting a statistically significant effect there is one (or more) which shows no significant effect.

Theoretically, immunotherapy has several advantages over chemotherapy. It may be effective in minimal residual disease if tumor cells are in the G0 phase. So-called kinetic refractoriness (see separate chapter in this volume) may not apply to immunotherapy. Finally, tumor cells appear to be more sensitive than normal cells to some cytotoxic mechanisms which form a part of the biological response to tumors.

Department des Maladies Sanguines et Tumorales & ICIG (Université Paris-Sud, CNRS UA 1163), Hôpital Paul-Brousse, 94804-Villejuif, France

Division of Hematology, Karolinska Hospital, S-10401 Stockholm, Sweden

TUMOR PROMOTION

Let us call cancer cells, cells which have undergone malignant transformation (1), probably along several steps, one of the

most important being the modification of a normal gene into an activated 'oncogene' (2). This can be the consequence of several possible, especially viral (3), chromosomal (4) or chemical accidents (5). These cells may for a time behave like saprophytic, pathogenic microbes (6), as a result of an equilibrium between their tendency to proliferate and the immunosurveillance of the host (7,8).

This equilibrium is disturbed if there is a proliferation promotion and/or an immunological control defect. Cancer cells may thus escape because of a proliferative 'promotion' event (9,10) in the two step oncogenesis scheme (11–13), or possibly because of differentiation (14) or disturbances in the cell communication (15) mechanism (17,18).

TUMOR REMISSION

Tumors can disappear after surgical and/or radiological or chemotherapeutic interventions—so-called complete remissions. However, usually some cancer cells persist and constitute a residual, minimal imperceptible tumor (19,20).

The present purpose is not to discuss the cell heterogeneity (21), anatomical sanctuaries (22), chemotherapy (24) resistance, or any other reasons for escape from the primary treatment, but to discuss the residual tumors.

MINIMAL RESIDUAL TUMORS AND ADJUVANT TREATMENT

That residual imperceptible disease occurs is shown by the high incidence of relapses and by the fact that relapses may or may not be caused by cells which carry the initial phenotype (25).

Tumor relapses are frequently seen after local surgery in the case of breast carcinoma (26,27) and that of other solid tumors such as cancers of the stomach, colon, rectum, pancreas, liver and lung. They are also frequent after radiotherapy of gliomas, head and neck and lung tumors (28).

Adjuvant radiotherapy

Generally, the incidence of metastases is not reduced by adjuvant radiotherapy (29,30), which can sometimes cause adverse effects (31,32). Nor does adjuvant radiotherapy increase the number of cures of stage III Hodgkin's disease (33). It does, however, prevent the incidence of local metastases after surgery of mammary carcinoma.

Adjuvant surgery

Adjuvant or 'second look' surgery is efficient in ovarian carcinoma (35,36).

Intensification chemotherapy

Relapses occur almost invariably in chronic myeloid (39) or lymphatic leukemias (39), myeloma (39) and small cell non-Hodgkin's lymphoma (39).

The relapse incidence can be reduced by the intensity of remission induction chemotherapy in acute or rapidly growing neoplasias, for example embryonic tumors such as placental (41) and testis choriocarcinomas (42) in adults, or in acute lymphatic leukemia (ALL) (40) in children and in acute myeloid leukemia in man.

It is conceivable that the large number of cells in the DNA synthesis phase in these acute neoplasias allows more cells to be killed by the cytostatics, known to be active on cells in cycle (43,44).

Adjuvant chemotherapy

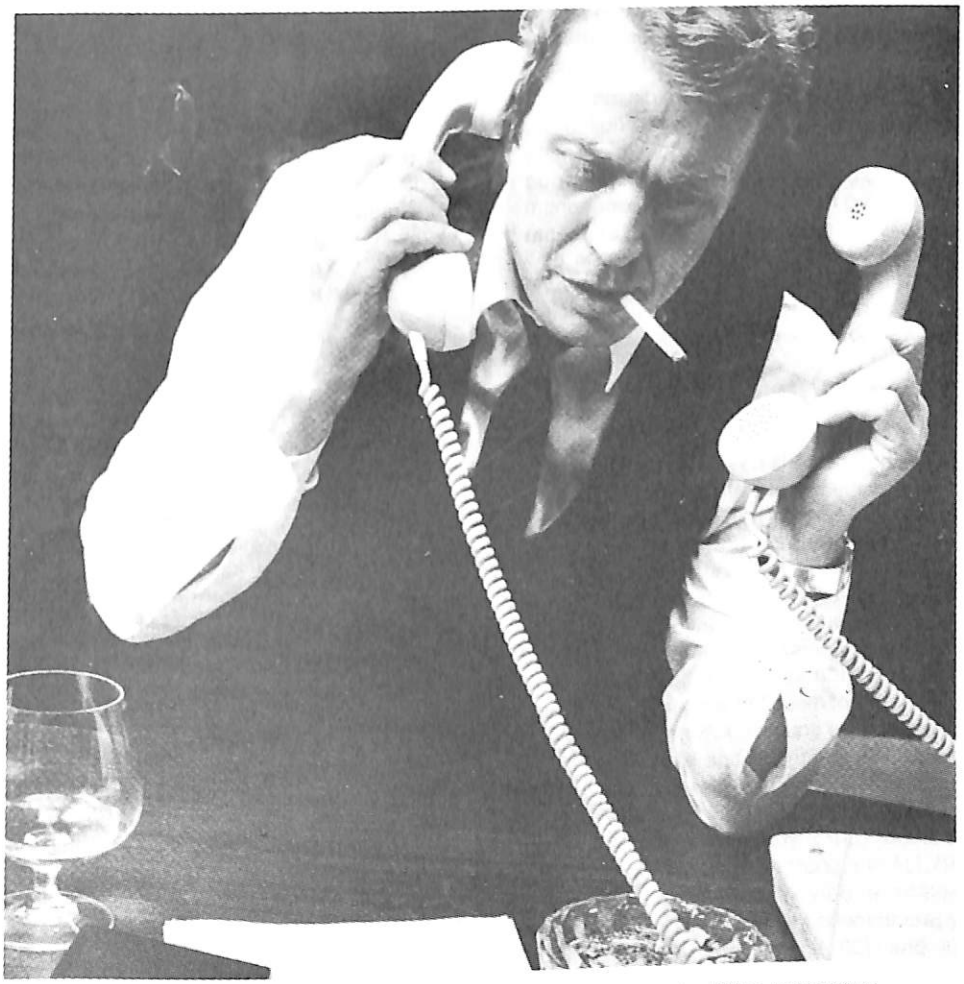
In contrast to induction chemotherapy, maintenance treatment has weak effects. It is true that pre- and post-surgical radiochemotherapy is effective in Ewing's tumor. Prolonged adjuvant chemotherapy (54) appears to play no beneficial role, however, in chronic or slowly growing tumors. Maintenance longer than 6 months is of uncertain benefit in ALL (45), Hodgkins disease (55–57), AML (46–53) and placental (41) and testis carcinomas (42). In large-cell non-Hodgkin lymphoma (NHL), a 1 year duration of maintenance chemotherapy may even be worse than only 6 months of chemotherapy (58–60).

Maintenance chemotherapy is also of uncertain benefit in chronic lymphatic leukemia (39),

BIOMAGNESIN®

Die Magnesiumtherapie bei erhöhtem Bedarf:

z. B. im Berufsstreß



Zusammensetzung: 1 Tablette enthält Magnesium hydrogenphosphoricum 265,0 mg, Magnesium citricum 66,0 mg, Acidum citricum 0,8 mg. **Anwendungsgebiete:** Bei allen Folgen eines Magnesium-Mangels, z. B. Gleichgewichtsstörungen (Schwindelgefühl), angstliche Übererregbarkeit, Schreckhaftigkeit, Krampfneigung der willkürlichen Muskulatur, Kopfschmerz, „Einschlafen" der Gliedmaßen, neuralgische Beschwerden. Biomagnesin wirkt ferner dämpfend bei gewissen Formen der beschleunigten und unregelmäßigen Herzschlagfolge und vorbeugend bei Neigung zu Nierensteinbildung (Oxalatsteine). Bei Thrombose-Gefahr und zur Thrombo-Embolie-Prophylaxe. **Darreichungsform und Packungsgröße:** O. P. mit 100 Tabletten (frei verkäuflich).

Vertretung für Luxemburg: Integral S. A.

Dr. Madaus GmbH & Co., 5000 Köln 91

MADAUS

myeloma (61,62), small cell non-Hodgkin lymphoma (NHL) (39,58) and chronic myelocytic leukemia (39,63). In ovarian carcinoma, the usually efficient chemotherapy (36,78) does not lead to complete remission. Adjuvant chemotherapy has not been shown, by a valid comparative trial (88), to be efficient in osteosarcoma.

In polycythemia vera, continuous treatment does much less well (64) than the discontinuous remission induction (65). Nor has the usefulness of maintenance chemotherapy been demonstrated in soft tissue sarcomas (66), melanoma (67), glioma (68), head and neck tumors (69), lung cancers (70) including the small cell type (71), stomach (72) and colon (73–75) carcinomas, prostate (76), uterus (77) and breast carcinoma in post-menopausal (79–82) and, in some trials, also in pre-menopausal patients as far as survival is concerned (82).

Pre-menopausal breast cancer

In addition to Ewing's tumor, pre-menopausal breast cancer may be the exception to the rule (90–92). Here, maintenance chemotherapy may in fact increase the disease-free survival (DFS) and, in some trials, the life expectancy. This has been shown by Nissen-Meyer (83), Donegan (84) and Fisher (85) with one cytostatic, and by Rossi (79) with the combination of cyclophosphamide, methotrexate and 5-fluoro-uracil (CMF). An oncofrance study (80,81) obtained a still better DFS with the combination adriamycine, vincristine, cyclophosphamide and 5-fluoro-uracil (AVCF), but no increased survival at 5 years (81). In the pre-menopausal patients, a 1 year duration of CMF does not seem to work better than a 6 month treatment (89). In fact, 1 year of CMF even seems to give a non-significantly less good result than a 6 month treatment (89). It therefore is not impossible that prolonged adjuvant chemotherapy may in fact be harmful, as has been suggested in non-Hodgkin lymphoma (58).

Post-menopausal breast cancer

Maintenance chemotherapy appears to be inefficient after the menopause. Bonadonna (86) has suggested that a reduction of CMF doses after the menopause could explain the absence of a chemotherapy effect. However, we found the same absence of an effect at the same age, although we applied the same AVCF doses as before the menopause (80,81). Similarly, no dose decrease in post-menopausal adjuvant chemotherapy was found either by the Ludwig Group (87) or by Howell et al. (82). Howell et al. (82) and Goldstein and Wabb (93) have, in fact, criticised the use of adjuvant chemotherapy in all forms of breast cancer.

It is possible that the absence of estrogen promotion of growth could explain the failure after the menopause. For instance, a relation between the effect of CMF on the DFS before menopause and the incidence of progesterone receptors has been found on tumor cells. There was a correlation between the DFS and the amenorrhea during chemotherapy (82). AVCF, which is superior to CMF for DFS in pre-menopausal patients, induced amenorrhea in all patients (81).

Acute leukemia

Early trials in 1961–63 showed, for example in ALL, that maintenance treatment with 6-mercaptopurine (6-MP) (94) or 6-MP combined with methotrexate (95) increased the length of the disease-free survival (DFS). This was at a time when there was no cure of ALL; remission induction therapy was poor. Today, when we have efficient induction chemotherapy, maintenance chemotherapy may not increase the cure rate (96). It does not seem to increase that of any of the three subgroups of patients with low, intermediate and high risks (96). It even reduces the cure rate in the standard risk group in our experience (97). Similarly, central nervous system radiotherapy (100) does not appear to be beneficial any longer in ALL (98). In contrast, radiotherapy may do neurological harm (99). Similarly, adjuvant chemotherapy in small cell lung carcinoma (102) and lung irradiation in osteosarcoma (88) no longer seems efficient. Again, these recent results contradict initial evaluations (101,103).

One of several possible explanations of these findings is that maintenance or adjuvant

chemotherapy might, in the earlier studies have been working only on the most sensitive cells (43,44), leaving relatively insensitive cells to respond to maintenance treatment. The residual tumor cells remaining after today's efficient induction treatment, on the other hand, also seem to be insensitive to maintenance treatment.

Non-Hodgkin lymphoma (NHL)

Maintenance treatment in large cell NHL does not improve the final prognosis (58), suggesting that the persisting cells survive because they are resistant. Cytostatics normally effective for induction treatment of stage I or stage II Hodgkin's disease are also effective as re-induction of patients who relapse after radiotherapy, if radiation was initially applied alone (117). The chemotherapy re-induction result is less efficient if chemotherapy is given even in the initial stage. Similarly, in AML, aclacinomycin gives a high incidence of second remissions when the first remission was induced without aclacinomycin (129,130). Similarly, almost 100% second responses are seen if myeloma patients without maintenance treatment are reinduced, but only 18% are seen in patients who had maintenance treatment, even if re-induction is performed with cytostatics not previously used (130a). A similar phenomenon is also seen in testis carcinoma (42).

Conclusion about maintenance chemotherapy

A reduction in the number of side effects and secondary leukemias (118) and other secondary malignancies (119,120), of chromosomal abnormality (121,122), as well as of patient discomfort (123) and sterility may be achieved (124,125) if maintenance chemotherapy is not routinely given.

Minimal residual tumors and immunotherapy

Acute lymphatic leukemia. When proposing active immunotherapy in 1968 (19,137) we have shown, in animal experiments, that cells in the G_0 or G_1 phases (138) are the most sensitive. In fact, the neoplastic cells of minimal residual disease may well be in G_0, since it has been shown that hematological malignancies may have prolonged average generation time (138a). However, immunotherapy provoked controversy for many reasons.

First, the tumor-associated antigens (TAA), demonstrated in experimental tumors by Foley (139) and Prehn (140), could be found in human tumors neither by Hewitt (141) nor by Baldwin (142).

The availability of monoclonal antibodies today has resulted in many reports about TAA, usually related to cell differentiation and possibly to oncogene activation (146), in both animal and human tumors (143). However, tumor cell heterogeneity (143a), maturation asynchrony (143b) and lineage infidelity (143c) render tumor-associated antigens ineffective in tumor surveillance. Moreover, such antigens may not be required for the cytotoxic activity of NK-cells (144), macrophages (8), or other cytotoxic cells (145).

Second, several clinical immunotherapy results have been controversial. Nevertheless, there are suggestions that even the primitive first generation immunotherapy can improve DFS and survival in ALL (152,153). In 1969 (152), no ALL-patients had been cured. Seven cures out of 20 patients was at that time significant. A genetic selection of the patients occurred with immunotherapy (154,155). A comparative trial with historical controls (45) and one randomized study (156) seemed to confirm the first results, but there are several negative trials as well. Stratification (157), multicentricity (157,159) and inequal patient numbers in the treatment (158) are discussed elsewhere (20). One trial had 27 participating centers for 300 patients and five treatment arms. In three of these arms there were 153 patients, which means 1.88 patients per arm per center (157). Another trial had 18, 52 and 52 patients in three treatment arms.

Chronic leukemia and lymphoma. In chronic lymphatic leukemia, Binet et al. (160) have recently published data which record a significant improvement after levamisole treatment. Salmon (161) has reported the same in myeloma.

In large cell non-Hodgkin's lymphoma, Hoerni (162) and Jones (163,164) still report significant benefits of BCG treatment with several years of follow-up, but here also other negative results exist. In AML (165,166), BCG initially prolonged remission duration and survival, and so did bestatine (167).

In CML (168) and melanoma (169,170) benefits have also been reported, but, again, many negative reports exist.

Carcinomas

In bronchial carcinoma, benefits were found by Maver et al. with intrapleural BCG (175), by Yasumoto and Yamamura with a cell wall substance (N.CWS,176), by Stewart et al. with an antigenic preparation (177) and by Focan et al. (178) with levamisole.

In gastric cancer, Ochial (179) found a significant benefit with N.CWS which is associated, as was the one we observed in our first ALL study (154,155), with a genetic selection (179).

In colon cancer, Robinson (180) obtained a benefit with a methanol residue (MER) of a BCG extract. In bladder cancer, local immunotherapy has been effective in several phase II trials (181).

In ovarian carcinoma, Albert (182) found favorable results after immunotherapy. In cervical carcinoma, Okamura (77) has registered a significant benefit, in breast carcinoma, Lacour (183,184), and in prostatic carcinoma, Edsmyr (151).

Second generation immunotherapy

Experimentally, minimal residual tumor cells seem to be sensitive to adoptive immunotherapy (188) as well as to cells mediating the graft versus leukemia reaction (189) or possibly the graft versus leukemogenic virus (190) reaction. The results of Weiden et al. (191) and other groups (192) tend to confirm this in man, as do the recent results with NK-like cells and lymphokine-activated killer (LAK) cells.

The possible role of hormones

Minimal residual tumors have been shown by Fisher (193) to be sensitive to hormonotherapy with anti-estrogens, but only in post-menopausal breast cancer with female hormone receptors. In contrast, estrogens reduce the survival of patients with prostatic carcinoma because of vascular complications (127).

CONCLUSION

It is not self-evident at present that maintenance chemotherapy is more effective in containing or eradicating minimal residual tumors than are the various attempts to use or activate the biological response to the tumor. There are indications that this latter response is mediated by antigen-independent cytotoxic cells. This cell population may include the cells responsible for the graft versus leukemia reaction.

REFERENCES

1. MONNAT R. J. Jr and LOEB L. A.: Mechanisms of neoplastic transformation. Cancer Invest. 1, 175-183, 1983.
2. COOPER G. M.: Cellular transforming genes. Science 217, 801, 1982.
3. FIELDS B. N. and GREENE M. I.: Genetic and molecular mechanism of viral pathogenesis: implications for prevention and treatment. Nature 300, 19-23, 1982.
4. YUNIS J. J.: The chromosomal basis of human neoplasia. Science 221, 227, 1983.
5. EVA A. and AARONSON S. A.: Frequent activation of C-KIS as a transforming gene in fibrosarcomas induced by methylcholanthrene. Science 220, 955-956, 1983.
6. SMITH H. and PEARCE J. H.: Microbial pathogenicity in man and animals. 22nd Symposium of the Society for General Microbiology. Cambridge, Cambridge University Press, 1972.
7. OLSSON L., MATHÉ G. and REIZENSTEIN P.: The biologic and immunologic response to tumors, in KUMMERLE H. H. (ed): Clinical Chemotherapy, vol. III; BERKADA B., KARRER K. and MATHÉ G. (eds): Antineoplastic Chemotherapy, pp. 308-319. New York, Thieme-Stratton, 1984.

8. CRISS W. E., ONO T. and SABINE J. R.: *Control Mechanisms in Cancer.* New York, Raven Press, 1976.

9. BERENBLUM I.: A speculative review: the probable nature of promoting action and its significance in the understanding of the mechanism of carcinogenesis. Cancer Res. 14, 471-477, 1954.

10. DIAMOND L., O'BRIEN T. G. and BAIRD W. M.: Tumor promoters and the mechanism of tumor promotion. Adv. Cancer Res. 32, 1-74, 1980.

11. IVERSEN O. H. and ASTRUP E. G.: The paradigm of two stage carcinogenesis: a critical attitude. Cancer Invest. 2, 51-60, 1984.

12. SCHWARTZ R. S.: Epstein-Barr virus —oncogen or mitogen? New Engl. J. Med. 302, 1307-1308, 1980.

13. MARX J. L.: Do promotors affect DNA after all? Science 219, 158-159, 1983.

14. DIAMOND L., O'BRIEN T. G. and ROVERA G.: Tumor promotors inhibit terminal cell differentiation in culture, in SLAGA T. J., SIVAK A. and BOUTWELL R. K. (eds): Carcinogenesis, vol. 2, pp. 335-342. New York, Raven Press, 1978.

15. FITZGERALD D. J. and MURRAY A. W.: Inhibition of intercellular communication by tumor-promoting phorbol esters. Cancer Res. 40, 2935-2937, 1980.

16. MURGITA R. A. and TOMASI R. B. Jr: Suppression of the immune response by α-fetoprotein. I. The effect of mouse α-fetoprotein on the primary and secondary antibody response. J. exp. Med. 141, 269-286, 1975.

17. COLE W. H. Dissemination of cancer: the need for stimulation of the immune process during the immunosuppression produced by major operations. South. Med. J. 75, 1479-1486, 1982.

18. JONES S. E., GRIFFITH K., DOMBROWSKI P. and GAINES J. A.: Immunodeficiency in patients with non-Hodgkin lymphomas. Blood 49, 335-344, 1977.

19. MATHÉ G.: Cancer active immunotherapy: immunoprophylaxis and immunorestoration. An introduction. Berlin, Springer, 1976.

20. MATHÉ G., ERIGUCHI M. and REIZENSTEIN P.: Cancer Residual Disease and its Adjuvant Chemotherapy and Immunotherapy. Do we Cure Cancer? Amsterdam, in press.

21. OLSSON L. and MATHÉ G.: Antigenic heterogeneity of leukemia. Blood Cells 7, 281-286, 1981.

22. EVANS A. E., GILBERT E. S. and ZANDSTRA A.: The increasing incidence of central nervous system leukemia in children. Cancer 26, 404-409, 1970.

23. MOLLER G. and MOLLER E.: The concept of immunological surveillance against neoplasia. Transplantn. Rev. 28, 3-15, 1976.

24. SELBY P.: Acquired resistance to cancer chemotherapy. Br. Med. J. 288, 1252-1253, 1984.

25. ZUELZER W. W., INOUE S. and THOMPSON R. I.: Long-term cytogenetic studies in acute leukemia in children: the nature of relapse. Am. J. Hemat. 1, 143, 1976.

26. BRINKLEY D. and HAYBITTLE J. L.: Long-term survival of women with breast cancer. Lancet 1, 1118, 1984.

27. HIBBERD A. D., HORWOOD L. J. and WELLS J. E.: Long-term prognosis of women with breast cancer in New Zealand: a study of survival to 30 years. Br. Med. J. 296, 1777, 1983.

28. EASSON E. C. and RUSSELL M. H.: The Curability of Cancer in Various Sites, p. 59. London, Pitman Medical.

29. OncoFrance, Projet 'Essais Comparatifs'. L'absence d'effet de la radiothérapie post-opératoire appliquée avant la chimiothérapie adjuvante dans le cancer du sein. Presse Med., in press.

30. BUZDAR A. U., BLUMENSCHEIN G. R., SMITH T. L., POWELL K. C., HORTOBAGYI G. N., YAP H. Y., SCHELL F. C.,

BRONCHODILATATION

Duovent®

EQUILIBREE

BOEHRINGER INGELHEIM

484/B/frz

un produit issu de notre recherche

Duovent®

aérosol doseur

fenoterol + ipratropium

le bronchodilatateur à double action

Composition
Une bouffée contient 0,1 mg de bromhydrate de fenoterol et 0,04 mg de bromure d'ipratropium

Propriétés
Le fenoterol est un bronchospasmolytique puissant stimulant les récepteurs bêta-2-adrénergiques. Il agit sélectivement au niveau de la musculature bronchique et utérine. Ses effets cardio-vasculaires sont faibles. De plus, le fenoterol stimule le transport mucociliaire et exerce un effet anti-allergique. En inhalation par aérosol-doseur (Berotec®), la dose unitaire recommandée est de 0,2 mg (c'est-à-dire une bouffée).
L'ipratropium est un bronchospasmolytique à effet parasympathicolytique qui inhibe la bronchoconstriction réflexe induite par le vague ; contrairement à l'atropine, l'ipratropium n'agit pas au niveau du système nerveux central, du fait de la présence dans sa structure chimique d'un groupement ammonium quaternaire. Par inhalation, une très faible dose suffit pour relâcher la musculature bronchique (la dose unitaire délivrée par l'aérosol-doseur d'Atrovent® est de 0,02 mg et la dose recommandée (en 1 fois) est de 0,04 mg) ; une telle dose n'induit pas d'effets secondaires systémiques de type anticholinergique tels que sécheresse buccale ou troubles de l'accommodation visuelle ; par ailleurs, elle est sans influence sur la sécrétion bronchique et la fonction mucociliaire. D'autre part, lorsqu'on en accroît les doses, l'ipratropium dispose encore d'une marge de sécurité particulièrement étendue.
Le Duovent associe le fenoterol et l'ipratropium.
Grâce à leur mode d'action différent, chacun des composants exerce un effet complémentaire.
En pathologie bronchique, il en résulte un élargissement du spectre thérapeutique de la médication et une diminution du taux de non-répondeurs à chacune des composantes. En effet, le bronchospasme peut être influencé quel qu'en soit le mécanisme : sympathique ou para-sympathique, allergique ou non.
La présence de fenoterol se traduit par une entrée en action immédiate de l'effet bronchodilatateur, qui apparaîtrait plus lentement sous ipratropium seul.
La durée de l'effet thérapeutique varie entre 4 et 8 heures, en fonction du degré de sévérité des bronchospasmes.
Des études de pharmacologie animale ont montré que le rapport optimal des 2 drogues dans l'association est de 2,5 pour le fenoterol et de 1 pour l'ipratropium.
L'aérosol-doseur de Duovent délivre par bouffée : 0,100 mg de fenoterol et 0,040 mg d'ipratropium.
Ainsi, l'adjonction d'ipratropium au fenoterol permet une réduction de moitié du dosage du fenoterol habituellement admis, tout en garantissant le maintien d'un effet thérapeutique au moins équivalent.
Il en résulte aussi une diminution de la fréquence et de l'intensité des effets secondaires du fenoterol.

Indications
- Traitement ou prévention du bronchospasme dans les bronchopneumopathies obstructives, telles que l'asthme bronchique, la bronchite chronique, l'emphysème pulmonaire, les pneumoconioses.
- Pré-traitement (ouverture des voies respiratoires) avant l'inhalation d'aérosols d'antibiotiques, de mucolytiques, de corticostéroïdes, de cromoglycate disodique ou de dérivés de la théophylline.

Contre-indications
Thyréotoxicose
Sténose hypertrophique idiopathique sous-aortique
Hypertrophie prostatique

Précautions particulières
On utilisera le Duovent avec prudence dans les affections cardiaques accompagnées de tachycardie ou de tachyarythmies. On évitera la prescription simultanée d'autres substances sympathicomimétiques.

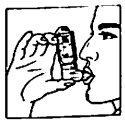
Utilisation au cours de la grossesse
Bien qu'aucun effet délétère ne soit apparu chez l'animal, on évitera par principe d'administrer le Duovent durant les trois premiers mois de la grossesse.
Au cours de la période précédant immédiatement l'accouchement, il convient de tenir compte du fait que le fenoterol exerce également un effet tocolytique.

Effets secondaires
Au dosage recommandé, on ne constate qu'exceptionnellement des effets secondaires de type sympathicomimétique et pratiquement aucun effet secondaire de nature anticholinergique.
A dose élevée, ou chez des patients présentant une sensibilité particulière aux sympathicomimétiques, on pourra observer des tremblements digitaux, des palpitations ou de l'agitation.
Rarement, on voit survenir, à titre de réaction locale, une sécheresse buccale ou, en cas de projection dans les yeux, des troubles modérés et réversibles de l'accommodation visuelle.

Surdosage et antidote
En cas d'intoxication par une dose massive, les symptômes principaux de surdosage sont essentiellement de caractère sympathicomimétique. On administrera dès lors en tant qu'antidote spécifique une substance bêta-lytique. Dans ce cas, il faut toutefois prendre en considération l'éventualité d'une aggravation de l'obstruction bronchique chez des patients souffrant d'une affection bronchospastique.

Posologie
Adultes et enfants au-dessus de 6 ans : 1 bouffée, à répéter éventuellement après 5 minutes. L'inhalation d'une telle dose peut être pratiquée à intervalles de 4 à 6 heures en moyenne ; l'on ne dépassera pas une dose totale de 6 doubles bouffées réparties sur 24 heures. Comme dose d'entretien moyenne, on administrera 1 ou 2 bouffées 3 à 4 fois par jour.
L'administration aux enfants se fera sous la surveillance d'un adulte.

Mode d'emploi
1. Enlever le capuchon de protection de l'embout plastique.
2. Agiter l'appareil (voir schéma) avant chaque emploi.
3. Prendre l'appareil entre deux doigts : l'index sur le fond de la cartouche en aluminium et le pouce sur l'embout. La flèche de l'étiquette est ainsi dirigée vers le haut.
4. Expirer à fond.
5. Serrer l'embout plastique avec les lèvres (voir schéma).
6. Inspirer par la bouche le plus profondément possible tout en exerçant une pression sur le fond en aluminium de l'appareil : il y a libération d'une bouffée d'aérosol. Retenir la respiration quelques secondes.
7. Retirer l'embout de la bouche, puis expirer lentement.
8. Remettre le capuchon de protection.



L'opacité du flacon ne permet pas de contrôler le niveau du liquide. Aussi faut-il l'agiter pour en vérifier la présence. Dès qu'il paraît vide, la soupape peut encore fonctionner efficacement une dizaine de fois.
L'embout buccal doit être conservé dans un parfait état de propreté. Il peut être nettoyé facilement à l'eau chaude savonneuse et rincé à l'eau claire.
L'aérosol-doseur de Duovent est sous pression : il ne peut être ouvert avec violence ni exposé à des températures supérieures à 50 °C.

Présentation
Aérosol-doseur : cartouche avec embout buccal contenant 30 mg de fenoterol et 12 mg de bromure d'ipratropium (300 doses).

Validité
2 ans

Formule
(8r)-3α-hydroxy-8-isopropyl-1αH,5αH-tropaniumbromid-(-)-tropasmonohydras 0,012 g, 1-(3,5-dihydroxyphenyl)-2-[[1-(4-hydroxybenzyl)-aethyl]amino]-aethanol hydrobromid 0,03 g, Sorbitan trioleas, Monofluorotrichloromethan, Difluorodichloromethan, Tetrafluorodichloroaethan q.s. pro 15 ml (= 300 bouffées dosées).

n.v. Boehringer Ingelheim s.a.
rue du Collège St-Michel 17
1150 Bruxelles – Tél. 02/762 56 55

BARNES B. C., AMES F. C., MARTIN R. G. and HERSH E. M.: Adjuvant chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide, with or without Bacillus Calmette-Guérin and with or without irradiation in operable breast cancer. A prospective randomized trial. Cancer 53, 384-389, 1984.

31. HOLLAND J. F., GLIDEWELL O. and COOPER R. G.: Adverse effect of radiotherapy on adjuvant chemotherapy of carcinoma of the breast. Surg. Gynec. Obstet. 150, 817-821, 1980.
32. STJERNSWARD J.: Possible drawback of radiotherapy: rational and experimental bases of post-surgical therapies, in BONADONNA G., MATHÉ G. and SALMON S. E. (eds): Adjuvant Therapies and Markers of Post-surgical Minimal Residual Disease I: Markers and General Problems of Cancer Adjuvant Therapies, pp. 115-118. Berlin, Springer, 1979.
33. GROZEA P. N., DE PERSIO E. J., COLTMAN C. A. Jr, FABIAN C. J., MORRISSON F. S., GEHAN E. A. and JONES S. E.: A Southwest Oncology Group: chemotherapy versus chemotherapy plus radiotherapy ion treatment of stage III Hodgkin's disease, in MATHÉ G., BONADONNA G. and SALMON S. (eds): Adjuvant Therapies of Cancer, pp. 83-91. Berlin, Springer, 1982.
34. VOLTERRANI F. and SIGURTA D.: Long-term costs of adjuvant radiotherapy, in MATHÉ G, BONADONNA G. and SALMON, S. (eds): Adjuvant Therapies of Cancer, pp. 310-311. Berlin, Springer, 1982.
35. BRUCKNER H. W., COHEN C. J., GOLDBERG J., KABAKOW B., WALLACH R. C., DEPPE G., REISMAN A. Z., GUSBERG S. and HOLLAND J. F.: Cisplatin regimens and improved prognosis of patients with poorly differentiated ovarian cancer. Am. J. Obstet. Gynec. 145, 653-658, 1983.
36. MISSET J. L., MARNICH R., MICHEL G., GEORGE M., WOLFF J. U. P. and MATHÉ G.: Stratégie du traitement des adénocarcinomes de l'ovaire. Exploration chirurgicale, dite 'second look' après chimiothérapie. Nouv. Presse Med. 9, 1937-1939, 1980.
37. SLADE N. S., SIMMONS R. L. and YUNIS E.: Immunodepression effect after major surgery in normal patients. Surgery 78, 363, 1975.
38. BLOMGREN H., WASSERMAN J., BARAL E. and PETRINI B.: Evidence for the appearance of non-specific suppressor cells in the blood after local irradiation. Int. J. Radiat. Oncol. biol. Phys. 4, 249, 1978.
39. MATHÉ G., MISSET J. L., MACHOVER D., SCHWARZENBERG L., TIMUS M., JASMIN C., RIBAUD P. and MUSSET M.: Protocoles des traitements des leucémies et des lymphomes: vers l'escalade ou vers la réduction de l'intensité? Biomed. Pharmacother. 38, 13-32, 1984.
40. MATHÉ G., MISSET J. L., MACHOVER D. and DE VASSAL F.: Results of acute lymphoid leukemia chemotherapy intensification on the non-Burkitt's high risk patient prognosis. In preparation.
41. BAGSHAWE K. D.: Treatment of trophoblastic tumours. Ann. Acad. Sci. 5, 273-279, 1976.
42. EINHORN L. E. and DONOHOE J. S.: Improved chemotherapy in disseminated testicular cancer. J. Urol. 117, 65, 1976.
43. MATHÉ G. and KENIS Y.: La Chimiothérapie des Cancers; Leucémies, Hématosarcomes et Tumeurs Solides, 3rd edn. Paris, Expansion Scientifique Française, 1975.
44. CLARYSSE A., KENIS Y. and MATHÉ G.: Cancer Chemotherapy. Its Role in the Treatment Strategy of Hematologic Malignancies and Solid Tumors. Berlin, Springer, 1976.
45. MATHÉ G., DE VASSAL F., SCHWARZENBERG L., DELGADO M., WEINER R.,

GIL M. A., PENA-ANGULO J., BELPOMME D., POUILLART P., MACHOVER D., MISSET J. L., PICO J. L., JASMIN C., HAYAT M., SCHNEIDER M., CATTAN A., AMIEL J. L., MUSSET M., ROSENFELD C. and RIBAUD P.: Preliminary results of three protocols for the treatment of acute lymphoid leukaemia in children: distinction of two groups of patients according to predictable prognosis. Med. Ped. Oncol. 4, 17-27, 1978.

46. SAUTER C., BERCHTOLD W., FOPP M., GRATWOHL A., IMBACH P., MAURICE P., TSCHOPP L., VON FLIEDNER V. and CAVALLI F.: Acute myelogenous leukaemia: maintenance chemotherapy after early consolidation treatment does not prolong survival. Lancet 1, 379-382, 1984.

47. FOON K. A. and GALE R. P.: Controversies in the therapy of acute myelogeneous leukemia. Am. J. Med. 72, 963-972, 1982.

48. BUCKNER R., URBANITZ D., EMMERICH B., FISCHER J., HEINECKE A., HIDDEMANN W., PFREUNDSCHUCH M., RUHL H. and WENDT F.: Long-term remission in acute myelogenous leukaemia. Lancet 1, 571, 1984.

49. CHAMPLIN R., JACOBS A., GALE R. P., BOCCIA R., ELASHOFF R., FOON K. and ZIGHELBOIM J.: Prolonged survival in acute myelogenous leukaemia without maintenance chemotherapy. Lancet 2, 894-896, 1984.

50. CASSILETH P. A., BEGG C. B., BENETT J. M., BOZDECH M., KAHN S. B., WEILER C. and GLICK J. H.: A randomized study of the efficacy of consolidation therapy in adult acute nonlymphocytic leukemia. Blood 63, 843-847, 1984.

51. POWLES R. L., SELBY P. J., PALU G., MORGENSTERN G., MCELWAIN T. J., CLINK H. M. and ALEXANDER P.: The nature of remission in acute myeloblastic leukaemia. Lancet 2, 674-676, 1979.

52. VAUGHAN W. P., KARP J. E. and BURKE P. J.: Long chemotherapy-free remissions after single-cycle timed-sequential chemotherapy for acute myelocytic leukemia. Cancer 45, 859-865, 1980.

53. POWLES R.: Long-term remissions in acute myelogeneous leukaemia. Lancet 1, 800-801, 1984.

54. GOLDMAN A.: Ewing's sarcoma: treatment with high dose radiation and adjuvant chemotherapy, in MATHÉ G., BONADONNA G. and SALMON S. (eds): Adjuvant Therapies of Cancer, pp. 115-119. Berlin, Springer, 1982.

55. DE VITA V. T. and SERPICK A.: Combination chemotherapy in the treatment of advanced Hodgkin's disease. Proc. Am. Ass. Cancer Res. 8, 13, 1967.

56. DE VITA V. T., SIMON R. M., HUBBARD S. M., YOUNG R. C., BRÉARD C. W., MOXLEY J. H. III, FREI E. III, CARBONE P. P. and CANELLOS G. P.: Curability of advanced Hodgkin's disease with chemotherapy: long-term follow-up of MOPP treated patients at NCI. Ann. intern. Med. 92, 587-595, 1980.

57. LEPAGE E., FERME C., FRIJA J., GAYET B., CLOT P., D'AGAY M. F., GISSELBRECHT C., MARTY M. and BOIRON M.: Maladie de Hodgkin. Masses résiduelles histologiquement non évolutives. Presse Med. 13, 1766-1769, 1984.

58. MATHÉ G., GIL-DELGADO M., MISSET J. L., MACHOVER D., RIBAUD P. and MUSSET M.: Prognostic at 9 years of 181 patients with centrofollicular non-Hodgkin's lymphoma (NHL) submitted to both remission induction and maintenance chemotherapy. Submitted for publication.

59. DE VITA V. T. Jr, CANELLOS G. P., CHABNER B., SCHEIN P., HUBBARD S. P. and YOUNG R. C.: Advanced diffuse histiocytic lymphoma, a potentially curable disease. Lancet 1, 248-250, 1975.

60. LAURIA F., BACCARANI M., FIACCHINI M., FREZZA R., GOBBI M. and TURA S.:

5-year survey of methotrexate, cyclophosphamide (endoxan), and vincristine (MEV) therapy for advanced non-Hodgkin's lymphomas. Cancer Treat. Rep. 62, 1193-1197, 1978.

61. BERGSAGEL D. E. and RIDER W. D.: Plasma cell neoplasms, in DE VITA V. T. (ed): Cancer: Principles and Practice of Oncology. Philadelphia, J. B. Lippincott, 1982.

62. REIZENSTEIN P.: Chronic lymphoid leukemias and myeloma: chemotherapy, in MATHÉ G., REIZENSTEIN P. and DICATO, P. (eds): Therapeutical Trials in Oncology: Methods, Ethics, Results. Geneva, Bioscience Ediprint, in press.

63. MATHÉ G., SCHWARZENBERG L., MISSET J. L., HAYAT M., JASMIN C., RIBAUD P., DE VASSAL F., DELGADO M. and PRADET BALADE O.: The present state of 'curability' of leukaemias (including polycythemia vera), in TANNER E. and HEFTI M. L. (eds): Annals of Life Insurance Medicine, pp. 111-133. Berlin, Springer, 1980.

64. NAJEAN Y.: Polycythemia vera: chemotherapy and P32, in MATHÉ G., REIZENSTEIN P. and DICATO M. (eds): Therapeutical Trials in Oncology: Methods, Ethics, Results. Geneva, Bioscience Ediprint, in press.

65. HAANEN C., MATHÉ G. and HAYST M. (For the EORTC Leukemia and Hematosarcoma Cooperative Group): Treatment of polycythaemia vera by radiophosphorus or busulphan: a randomized trial. Br. J. Cancer 44, 75-80, 1981.

66. ROSENBERG S. A., TEPPER J., GLATSTEIN E., COSTA J., YOUNG R., SEIPP C. and WESLEY R. Adjuvant chemotherapy for patients with soft tissue sarcomas. Surg. Clin. N. Am. 61, 1415-1424, 1981.

67. BERETTA G.: Melanoma: chemotherapy, in MATHÉ G., REIZENSTEIN P. and DICATO M. (eds): Therapeutical Trials in Oncology: Methods, Ethics, Results. Geneva, Bioscience Ediprint, in press.

68. AFRA D., KOCSIS B., DOBAY J. and ECKHARDT S.: Combined radiotherapy and chemotherapy with dibromodulcitol and CCNu in the postoperative treatment of malignant gliomas. J. Neurosurg. 59, 106-110, 1983.

69. KRAMER S.: Methotrexate and radiation therapy in the treatment of advanced squamous cell carcinoma of the oral cavity, oropharynx, supraglottic larynx and hypopharynx. Can. J. Otolaryng. 4, 213-218, 1975.

70. HIGGINS G. A. and SCHIELDS T. W.: Experience of the Veterans Administration Surgical Adjuvant Group. Prog. Cancer Res. Ther. 11, 433-442, 1979.

71. ARNOLD A. M., WILLIAMS C. J., MEAD G. M., BUCHANAN R. B., GREEN J. A., MACBETH F. M. and WHITEHOUSE J. M.: Combination chemotherapy using high or low dose methotrexate for small cell carcinoma of the lung—a randomised trial. Med. Oncol. Tumor Pharmacother. 1, 9-14, 1984.

72. INOKUCHI K., HATTORI T., TAGUCHI T., ABE O. and OGAWA N.: Postoperative adjuvant chemotherapy for gastric carcinoma. Analysis of data on 1805 patients followed for 5 years. Cancer 53, 2393-2397, 1984.

73. Gastrointestinal Tumor Study Group: Adjuvant therapy of colon cancer. Results of a prospectively randomized trial. New Engl. J. Med. 310, 737-742, 1984.

74. LI M. C. and ROSS S. T.: Chemoprophylaxis for patients with colorectal cancer: prospective study with five-year follow-up. J. Am. Med. Ass. 235, 2825-2828, 1976.

75. LAWRENCE W., TERZ J. J. and HORSLEY S.: Chemotherapy as an adjuvant to surgery in colorectal cancer. Cancer Clin. Trials 1, 35-41, 1978.

75. LAWRENCE W., TERZ J. J. and HORSLEY S.: Chemotherapy as an adju-

vant to surgery in colorectal cancer. Cancer Clin. Trials 1, 35-41, 1978.

76. STEPHENS R. L., VAUGHN C., LANE M., COSTANZI J., O'BRYAN R., BALCERZAK S. P., LEVIN H., FRANK J. and COLTMAN C. A. Jr: Adriamycin and cyclophosphamide versus hydroxyurea in advanced prostatic cancer. A randomized Southwest Oncology Group Study. Cancer 53, 406-410, 1984.

77. OKAMURA K.: Uterus tumors, in MATHÉ G., REIZENSTEIN P. and DICATO M. (eds): Therapeutical Trials in Oncology: Methods, Ethics, Results. Geneva, Bioscience Ediprint, in press.

78. SMITH J. P. and RUTLEDGE F. N.: Chemotherapy in advanced ovarian cancer. Natn. Cancer Inst. Monogr. 42, 141-143, 1975.

79. ROSSI A., BONADONNA G., VALAGUSSA P. and VERONESI U.: Multimodal treatment in operable breast cancer: five year result of the CMF-programme. Br. Med. J. 282, 405, 1981.

80. MATHÉ G., MISSET J. L., PLAGNE R., BELPOMME D., GUERRIN J., FUMOLEAU P., METZ R. and DELGADO M. (OncoFrance Comparative Trial Project): Superiority of AVCF (adriamycin, vincristine, cyclophosphamide and 5-fluorouracile) over CMF (cycloph osphamide, methotrexate and 5-fluorouracile) as adjuvant chemotherapy for breast cancer. A phase III trial of Association OncoFrance, in TOSIRU and VOSHIDA (eds): Basic Mechanisms and Clinical Treatments of Tumor Metastasis. New York, Academic Press, in press.

81. MATHÉ G., MISSET J. L., PLAGNE R., BELPOMME D., LE MEVEL B., GUERRIN J., FUMOLEAU P., METZ R., DELGADO M., DE VASSAL F., ERIGUCHI M. and SCHNEIDER M. (OncoFrance Comparative Trial): Controlled phase III trial of breast cancer adjuvant chemotherapy comparing CMF and the combination of AVCF (adriamycin, vincristine, cyclophosphamide and 5-fluorouracile). Submitted for publication.

82. HOWELL A., BUSH H., GEORGE W. D., HOWAT J. M. T., CROWTHER D., SELLWOOD R. A., RUBENS R. D., HAYWARD J. L., BULBROOK R. D., PENTIMAN I. S. and VHAUDARY M.: Controlled trial of adjuvant chemotherapy with cyclophosphamide, methotrexate and fluorouracil for breast cancer. Lancet 2, 307-311, 1984.

83. NISSEN-MEYER R., KJEILGRAN K., MALMIO K., MANSONN B. and NORIN T.: Surgical adjuvant chemotherapy. Results with one short course with cyclophosphamide after mastectomy for breast cancer. Cancer 41, 2088-2099, 1978.

84. DONEGAN W. L.: Extended surgical adjuvant thiotepa for mammary carcinoma. Arch. Surg. 109, 187-192, 1974.

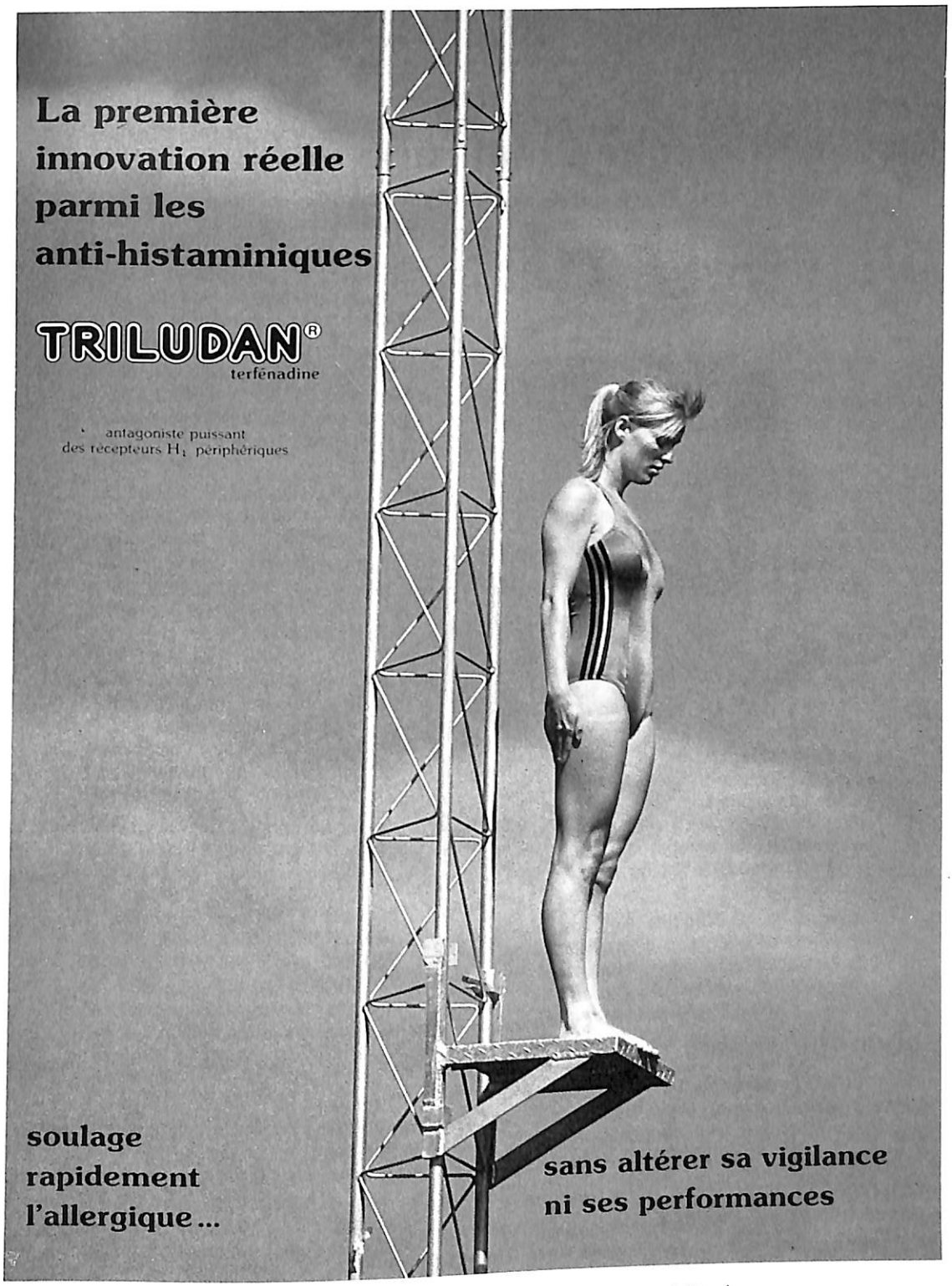
85. FISHER B., SLACK N., KATRYCH D. and WOLMARK N.: Ten year follow-up results of patients with carcinoma of the breast in a co-operative clinical trial evaluating surgical adjuvant chemotherapy. Surg. Gynec. Obstet. 140, 528-534, 1975.

86. BONADONNA G. and VALAGUSSI P.: Dose–response effect in adjuvant chemotherapy in breast cancer. New Engl. J. Med. 304, 10, 1981.

87. Ludwig Breast Cancer Study Group: Randomised trial of chemo-endocrine therapy, endocrine therapy, and mastectomy alone in postmenopausal patients with operable breast cancer and axillary node metastasis. Lancet 1, 1256-1260, 1984.

88. DELEPINE G., JASMIN C. and MATHÉ G.: Sarcomes ostéogènes. J. intern. Med. 9, 15-20, 1984.

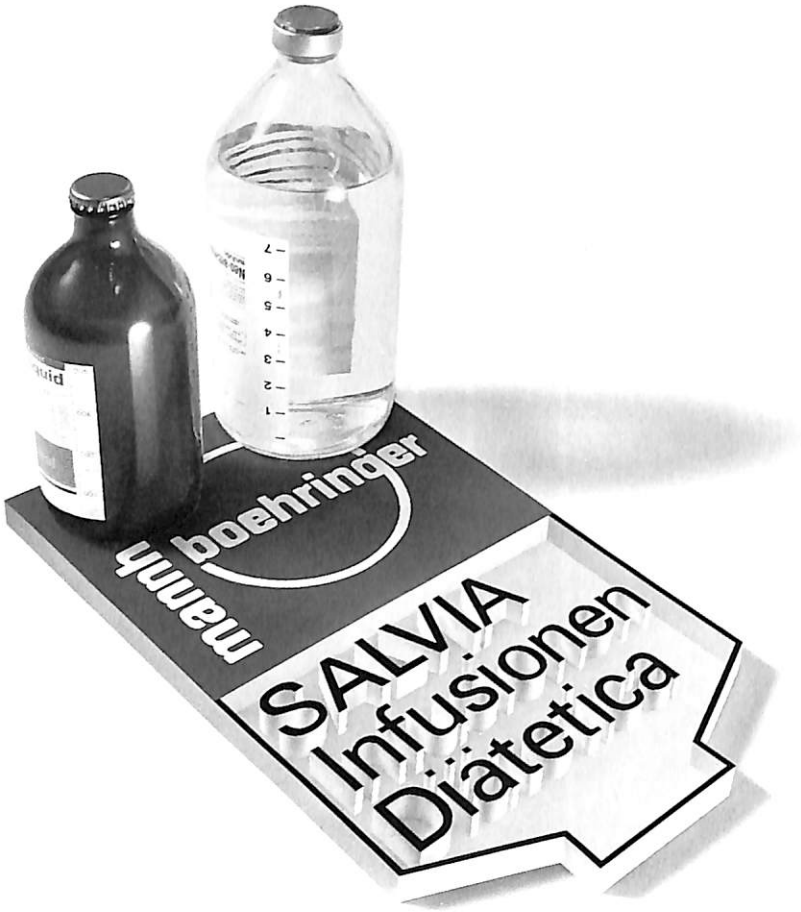
89. TANCINI G., BONADONNA G., VALAGUSSA P., MARCHINI S. and VERONESI U.: Adjuvant CMF in breast cancer: comparative 5-year results of 12 versus 6 cycles. J. clin. Oncol. 1, 2-10, 198£.



Triludan: Délivrance sur prescription médicale.

PROPHAC - Howald
5, Rangwé L-2412 Howald
Tél: 48 24 82

Kompetent
für die klinische Ernährung



Salvia-Infusionen

Das moderne Konzept für die parenterale Versorgung Ihrer Patienten

- Praxisgerechte Ernährungsregime
- Individuelle Kombinationsmöglichkeiten
- Umfassendes Programm

Salvia-Diätetica

Das komplette Programm für Ihre enterale Ernährungstherapie

- Innovative Produkte
- Vollwertige Ernährung
- Sichere Anwendungstechnik

Ihre speziellen Fragen beantworten wir gern.
Bitte schreiben Sie uns.

Salvia-Werk GmbH
D 6650 Homburg/Saar

90. ASKENASE P. W., HAYDEN N. J. and GERSHON R. K.: Augmentation of delayed type hypersensitivity by doses of cyclophosphamide which do not affect antibody responses. J. exp. Med. 141, 697, 1975.

91. ORBACH-ARBOUYS S. and CASTES M.: Augmentation of immune responses after methotrexate administration. Immunology 36, 265-269, 1979.

92. EHRKE M. J., RYOYAMA K. and COHEN S. A.: Cellular basis for adriamycin-induced augmentation of cell mediated cytotoxicity in culture. Cancer Res. 44, 2497-2504, 1984.

93. GOLDSTEIN G. and WEBB R. F.: Adjuvant chemotherapy in breast cancer: no news. Lancet 1, 816, 1983.

94. FREIREICH E. J., GEHAN E., FREI E. III, SCHROEDER L. R., WOLMAN I. J., ANBARI R., BURGERT E. O., MILLS S. D., PINKEL D., SELAWRY O. S., MOON J. H., GENDEL B. R., SPURR C. L., STORBS R., HAURANI F., HOOGSTRATEN B. and LEE S.: The effect of 6-mercaptopurine in the duration of steroid-induced remissions in acute leukemia: a model for evaluation of other potentially useful therapy. Blood 21, 699, 1963.

95. FREI E. III, FREIREICH E. J , GEHAN E., PINKEL D., HOLLAND J. F., SELWARY O., HAURANI F., SPURR C. L., HAYES D. M., JAMES G. W., ROTHBERG H., SODEE D. B., RUNDLES R. W., SCHROEDER L. R., HOOGSTRATEN, B., WOLMAN I. J., TRAGGIS D. G., COOPER T., GENDEL B. R., EBAUGH F. and TAYLOR R.: Studies of sequential and combination antimetabolite therapy in acute leukemia. 6-mercaptopurine and methotrexate. Blood 18, 431-454, 1961.

96. SACKMANN MURIEL F., SVARCH E., PAVLOVSKY S., BUSTELO P., GUINTOLI J., VERGARA B., GARAY G., EPPINGER-HELFT M., KVICALA R. and DIBAR E.: Alternating pulses of vincristine–prednisone with cytarabine–cyclophosphamide versus vincristine–prednisone in the maintenance therapy of acute lymphoblastic leukemia. Cancer Treat. Rep. 68, 581-586, 1984.

97. MATHÉ G., MISSET J. L. and MACHOVER D.: L'intensification de la chimiothérapie améliore le pronostic des leucémies aigues lymphoides à haut risque et détériore celui des formes à risque standard. Submitted for publication.

98. SULLIVAN M. P., CHEN T., DYMENT P. G., HVIZDALA E. and STEUBER C. P.: Equivalence of intrathecal chemotherapy and radiotherapy as central nervous system prophylaxis in children with acute lymphatic leukemia: a Pediatric Oncology Group Study. Blood 60, 948-958, 1982.

99. EISER C.: Intellectual abilities among survivors of childhood leukaemia as a function of CNS irradiation. Arch. dis. Child. 53, 391-395, 1978.

100. PINKEL D.: The Ninth Annual David Karnofsky Lecture. Treatment of acute lymphocytic leukemia. Cancer 48, 1128, 1979.

101. WHITEHOUSE J. M. A. and WILLIAMS C. J.: Metastatic CNS disease in small cell carcinoma of the bronchus: the role of radiotherapy and chemotherapy, in MATHÉ G., BONADONNA G. and SALMON, S. (eds): Adjuvant Therapies of Cancer, pp. 207-213. Berlin, Springer, 1982.

102. BUNN P. A. and IHDE D. C.: Small cell bronchogenic carcinoma: a review of therapeutic results, in LIVINGSTON B. B. (ed): Lung Cancer, pp. 169-208. The Hague, Martinus Nijkoff, 1981.

103. VEN DER SCHUEREN E. and BREUR J.: Role of lung irradiation in the adjuvant treatment of osteosarcoma, in MATHÉ G., BONADONNA G. and SALMON S. (eds): Adjuvant Therapies of Cancer, pp. 98-102. Berlin, Springer, 1982.

104. RAI K. R., HOLLAND J. F., GLIDEWELL O. J., WEINBERG V., BRUNNER K., OBRECHT J. P., PREISLER H. D.,

NAWABI I. S., PRAGER D., CAREY R. W., COOPER M. R., HAURANI F., HUTCHINSON J. L., SILVER R. T., FALKSON G., WIERNIK P., HOAGLAND H. C., BLOOMFIELD C. D., JAMES G. W., GOTTLIEB A., RAMANAN S. V., BLOM J., NISSEN N. I., BANK A., ELLISON R. R., KING F., HENRY P., MCINTYRE O. R. and KAAN S. K.: Treatment of acute myelocytic leukemia: a study by Cancer and Leukemia Group B. Blood 58, 1203-1212, 1981.

105. ARNOLD A. M., WILLIAMS C. J., MEAD G. M., BUCHANAN R. B., GREEN J. A., MACBETH M. and WHITEHOUSE J. M.: Combination chemotherapy using high or low dose methotrexate for small cell carcinoma of the lung. A randomized trial. Med. Oncol. Tumor Pharmacother. 1, 9-14, 1984.

106. STRENDER E., BLOMGREN H., PETRINI B., WASSERMAN, J., FORSGREN M., NORBERG R., BARAL E. and WALLGREN A.: Immunologic monitoring in breast cancer patients receiving postoperative adjuvant chemotherapy. Cancer 48, 1996-2000, 1981.

107. SMIT B., STJERNSWARD B., DOWDLE E., ROSSALL SEALY G., WILSON E., BEATTY D., JACOBS P. and BENETTE B.: The lymphocyte: monocyte ratio: B- and T-cell ratio after radiotherapy, chemotherapy and surgery. Int. J. Radiat. Oncol. biol. Phys. 5, 1841-1847, 1979.

108. LÉVI F. A., BLUM J. P., LEMAIGRE G., BOURUT C., REINBERG A. and MATHÉ G.: A four-day subrenal capsule assay for testing the effectiveness of anticancer drugs against human tumors. Cancer Res. 44, 2660-2667, 1984.

109. CHU A. M., COPE O., RUSSO R. and LEW R.: Patterns of loca-regional recurrence and results in stages I and II breast cancer treated by irradiation following limited surgery. An update. Am. J. clin. Oncol. 7, 221-229, 1984.

110. FREIREICH E. J., KARON M. and FREI E.: Combination chemotherapy of childhood leukemia with vincristine, amethopterin, mercaptopurine and prednisone (VAMP). Proc. Am. Ass. Cancer Res. 5, 50, 1964.

111. FREI E. and FREIREICH E. J.: Progress and perspectives in the chemotherapy of acute leukemia. Adv. Chemother. 2, 269-289, 1965.

112. FISHER R. I., DE VITA V. T. Jr, HUBBARD S. M., BRENNAN M. F., CHABNER B. A., SIMON R. and YOUNG R. C.: Pro-MACE-MOPP combination chemotherapy: treatment of diffuse lymphomas. Proc. Am. Soc. clin. Oncol. 16, 468, 1980.

113. GOLSTEIN D. P. and BERKOWITZ R.: The management of gestional trophoblastic neoplasm, in: Current Problems in Obstetrics and Gynecology, pp. 25-26. Chicago, Year Book, 1980.

114. MACHOVER D., RAPPAPORT H., SCHWARZENBERG L., MISSET J. L., GOLDSCHMIDT E., LEMAIGRE G., DORVAL T., DE VASSAL F., RIBAUD P., GAGET H. and MATHÉ G.: Treatment of acute myeloid leukemia with a combination of intensive induction chemotherapy, early consolidation splenectomy and long-term maintenance chemotherapy. Cancer 53, 1644-1650, 1984.

115. LONSDALE D., GEHAN E. A., FERNBACH D. J., SULLIVAN P. O., LANE D. M. and RAGAB A. H.: Interrupted vs continued maintenance therapy in childhood acute leukemia. Cancer 36, 341-352, 1975.

116. FREI E. III: Acute leukemia in children. Model for the development of scientific methodology for clinical therapeutic research in cancer. Cancer 53, 2013-2025, 1984.

117. PENE F., HENRY-AMAR M., LE BOURGEOIS J. P., HAYAT M., GÉRARD-MARCHANT R., LAUGIER A., MATHÉ G. and TUBIANA M.: A study of relapse and course of 153 cases of Hodgkin's disease (clinical stages I and II) treated at the Institut Gustave-Roussy from 1963

to 1970 with radiotherapy alone or with adjuvant monochemotherapy. Cancer 46, 2131-2141, 1980.

118. LERNER H. J.: Acute myelogenous leukemia in patients receiving chlorambucil as long-term adjuvant chemotherapy for stage II breast cancer. Cancer Treat. Rep. 62, 1135-1138, 1978.

119. NESBIT M., ROBINSON L., SATHER H., MEADOWS A., ORTEGA J. and HAMMOND D. for the Childrens Cancer Study Group (CCSG): Evaluation of long-term survivors of childhood acute lymphoblastic leukemia (ALL). Proc. Am. Ass. Cancer Res. 23, 107, 1982.

120. JACQUILLAT C., WEIL M., AUCLERC G., TEILLET F., WEISGERBER C., TANZER J., BOIRON M. and BERNARD J.: Les néoplasies simultanées et successives. A propos de 18 observations d'affections malignes compliquant l'évolution de la maladie de Hodgkin. Nouv. Presse Med. 2, 3039, 1973.

121. PATIL S. R., CORDER M. P., JOCHIMSEN P. R. and DICK F. R.: Bone marrow chromosome abnormalities in breast cancer patients following adjuvant chemotherapy. Cancer Res. 40, 4076-4080, 1980.

122. SEINO Y., NAGAO M., YAHAGI T., HOSHI A., KAWACHI T. and SUGIMURA T.: Mutagenicity of several classes of antitumor agents to Salmonella typhimurium TA98, TA100 and TA92. Cancer Res. 38, 2148-2156, 1978.

123. GOFF J. R., ANDERSON H. R. and COOPER P. F.: Diatractability and memory in long-term survivors of acute lymphocytic leukemia. J. Dev. Behav. Ped. 1, 158-163, 1980.

124. SHERINS R. J., OLWENY C. L. M. and ZIEGLER J. L.: Gynecomastia and gonadal dysfunction in adolescent boys treated with combination chemotherapy for Hodgkin's disease. New Engl. J. Med. 299, 12-16, 1978.

125. SHALET S. M.: Effects of chemotherapy on gonadal function of patients. Cancer Treat. Rev. 7, 141-152, 1980.

126. WEIL M., JACQUILLAT C., AUCLERC G., UNGER P. F. and BERNARD J.: Long-term cost of combined radiotherapy and chemotherapy, in MATHÉ G., BONADONNA G. and SALMON S. (eds): Adjuvant Therapies of Cancer, pp. 312-316. Berlin, Springer, 1982.

127. Veterans Administration Co-Operative Urological Research Group: Treatment and survival of patients with cancer of the prostate. Surg. Gynec. Obstet. 124, 1011-1017, 1967.

128. NEVASAARI K., HEIKKINEN M. and TASKINEN P. J.: Tamoxifen and thrombosis. Lancet 2, 946-947, 1978.

129. MATHÉ G., BAYSSAS M., GOUVEIA J., DANTCHEV D., RIBAUD P., MACHOVER D., MISSET J. L., SCHWARZENBERG L., JASMIN C. and HAYAT M.: Preliminary results of a phase II trial of aclacinomycin in acute leukaemia and lymphosarcoma. An oncostatic anthracyclin that is rarely cardiotoxic and induces no alopecia. Cancer Chemother. Pharmac. 1, 259-262, 1978.

130. MACHOVER D., GASTIABURU J., DELGADO M., GOLDSCHMIDT E., HULHOVEN R., MISSET J. L., DE VASSAL F., TAPIERO H., RIBAUD P., SCHWARZENBERG L. and MATHÉ G.: Phase I–II study of aclarubicin for treatment of acute myeloid leukemia. Cancer Treat. Rep. 68, 881-886, 1984.

130a. OSBY E., REIZENSTEIN P., MATHÉ G., PEETERMANS M., BLANC C., CAUCHIE C., FIERE D. and JAUBERT M.: Alternating and non alternating chemotherapy of myeloma. Anticancer Res. 5, 339-342, 1986.

131. MATHÉ G., CANON C., GOUTNER A., OGIER C. and REIZENSTEIN P.: The common acute lymphoid leukemia antigen in blood, bone marrow and lymph nodes in lymphoid malignancies at diagnosis and in remission. 5th International

Congress of Immunology, Kyoto, 21–27 August 1983.

132. CANON C., EICHLER-REISS F., REIZENSTEIN P. and MATHÉ G.: Difference between monoclonal antibodies against the common acute leukemia antigen from two different hybridomas. Anticancer Res. 3, 407-408, 1983.

133. BRÉARD J., CONSOLINI R. and MATHÉ G.: Does a cell abnormality persist after acute lymphoid leukemia cure? Lancet, in press.

134. HOLLAND J. F.: Breaking the cure barrier. J. clin. Oncol. 1, 75-90, 1983.

135. SATO G. H.: Cell culture, hormones and growth factors, in JIMENES DE ASUA L., LEVI-MONTALCINI R., SHIELDS R. and IACOBELLI S. (eds): Control Mechanisms in Animal Cells, pp. 1-4. New York, Raven Press, 1980.

136. TERRY W.: Cancer immunotherapy, in: Proceedings of the Paris Anti-Cancer Congress 1978, unpublished.

137. MATHÉ G.: Immunothérapie active de la leucémie L1210 après la greffe tumorale. Rev. Franç. Et. clin. Biol. 13, 881-883, 1968.

138. OLSSON L. and MATHÉ G.: A cytokinetic analysis of bacillus Calmette-Guérin induced growth control of murine leukemia. Cancer Res. 37, 1743, 1977.

138a. SKARBERG C., CEA R. and REIZENSTEIN P.: Cell proliferation rates in polycythemia vera. Acta Med. scand. 195, 307-311, 1974.

139. FOLEY E. J.: Antigenic properties of methylcholanthrene-induced tumors in mice of the strain of origin. Cancer Res. 13, 835, 1953.

140. PREHN R. T.: Tumor specific immunity to transplanted dibenz(a,h) anthracene induced sarcomas. Cancer Res. 20, 1614, 1960.

141. HEWITT H. B., BLAKE E. R. and WALDER A. S.: A critique of the evidence of host defense against cancer based on personal studies of 27 murine tumors of spontaneous origin. Br. J. Cancer 33, 241, 1976.

142. BALDWIN R. W., EMBLETON M. J. and PIMM M. V.: Immune responses to carcinogen-induced and spontaneous rat tumours, in SPREAFICO F. and ARNON R. (eds): Tumor-associated Antigens and Their Specific Immune response, p. 21. London, Academic Press, 1979.

143. HELLSTROM K. E., HELLSTROM I. and BROWN J. P.: Diagnostic and therapeutic use of monoclonal antibodies to human tumor antigens. Med. Oncol. Tumor Pharmacother. 1, 143, 1984.

143a. ANDRAESEN R., BIBERFELD P., OST A., REIZENSTEIN P. and OLSSON L.: Specificity of a panel of monoclonal antibodies against myeloid leukemia cells. Scand. J. Haemat. 37, 323-332, 1986.

143b. REIZENSTEIN P., OST A., SKOOG L., CHRISTENSON B., BIBERFELD P. and LAGERLOF B.: Maturation asynchrony in leukemic cells. Anticancer Res. 5, 361-362, 1985.

143c. REIZENSTEIN P., BEKSAC M., BIBERFELD P., CHRISTENSON B., LAGERLOF B., LAUREN L., OST A. and PORWIT A.: Leukemic myeloblasts expressing lymphoid markers. Acta Haemat. 74, 148-150, 1985.

144. TALMADGE J. E., MEYERS L. M., PRIEUR D. J. and STARKEY J. R.: Role of natural killer cells in tumor growth and metastasis: C57B1/6 normal and beige mice. J. natn. Cancer Inst. 65, 929, 1980.

145. OLSSON L., KIGER N. and MATHÉ G.: Autoreactive cells in cancer-active immunotherapy: their cytotoxic potential and genetic restriction. Transplantn. Proc. 12, 167-171, 1980.

146. KUZUMAKI N., MINAKAWA H., MATSUO T., HARAGUCHI S. and YOSHIDA T.: Correlation between tumor-specific surface antigens and *src* gene expression in Rous sarcoma virus-induced rat tumors. Eur. J. Cancer clin. Oncol. 19, 401, 1983.

147. O'HARA C. J. and PRICE G. B.: A monoclonal antibody demonstrating specificity for drug-resistant cells. Immun. Lett. 5, 15, 1982.

148. TERRY W. D. and WINDHORST D. (eds): Immunotherapy of Cancer: Present Status of Trials in Man. New York, Raven Press, 1978.

149. TERRY W. D. and ROSENBERG S. A. (eds): Immunotherapy of Human Cancer. Amsterdam, Elsevier North Holland, 1982.

150. MATHÉ G., MISSET J. L., SERROU B., JEANNE C., GUERRIN J., PLAGNE R., SCHNEIDER M., LE MEVEL B. and METZ R.: Immunotherapy versus chemoimmunotherapy as adjuvant treatment of malignant melanoma, in TOSIRU and YOSHIDA (eds): Basic Mechanisms and Clinical Treatments of Tumor Metastasis. New York, Academic Press, in press.

151. EDSMYR F., ESPOSTI P. L., ANDERSSON L., NASLUND I. and BLOMGREN H.: Clinical study on bestatin and peplomycin in treatment of prostatic carcinoma, in CARTER S. K. and ULTMANN J. (eds): Sy87-2 Peplomycin. 13th International Congress of Chemotherapy, Vienna 28 August–2 September 1983.

152. MATHÉ G., AMIEL J. L., SCHWARZENBERG L., SCHNEIDER M., CATTAN A., SCHLUMBERGER J. R., HAYAT M. and DE VASSAL F.: Active immunotherapy for acute lymphoblastic leukaemia. Lancet 1, 697-699, 1969.

153. LEE Y. J. and WESLEY R. A.: Statistical contributions to phase II trials in cancer: interpretation, analysis and design. Sem. Oncol. 8, 403, 1981.

154. TURSZ T., HORS J., LIPINSKI M., AMIEL J. L. and MATHÉ G.: Comparison of HLA phenotypes in long-term survivors with acute lymphoblastic leukemia treated with immunotherapy versus chemotherapy, in MATHÉ G., BONADONNA G. and SALMON S. (eds): Adjuvant Therapies of Cancer, p. 26. Berlin, Springer, 1982.

155. TURSZ T.: Heterogeneity of results correlated to genetics (HLA-DR), in MATHÉ G., REIZENSTEIN P. and DICATO M. (eds): Therapeutical Trials in Oncology: Methods, Ethics, Results. Geneva, Bioscience Ediprint, in press.

156. PAVLOVSKY S., SACKMANN MURIEL F., GARAY G., SVARCH E., BRAIER J., LAGARDE M., SCAGLIONE C., EPPINGER-HELFT M., FAILACE R. and DIBAR E.: Chemoimmunotherapy with levamisole in acute lymphoblastic leukemia. Cancer 48, 1500, 1981.

157. HEYN R. M., JOO P., KARON M., NESBIT M., SHORE N., BRESLOW N., WEINER J., REED A. and HAMMOND D.: BCG in the treatment of acute lymphocytic leukemia. Blood 46, 431-442, 1975.

158. Medical Research Council by the Leukaemia Committee and the Working Party on Leukaemia in Childhood: Treatment of acute lymphoblastic leukaemia. Comparison of immunotherapy (BCG), intermittent methotrexate, and no therapy after a five-month intensive cytotoxic regimen (Concord Trial). Br. Med. J. 4, 189-194, 1971.

159. REIZENSTEIN P., DELGADO M., GASTIABURU J., LOMME L., OGIER C., PALS H., SCHELLEKENS J., WHITTAKER J. and MATHÉ G.: Efficacy of and errors in randomized multicenter trials. A review of 230 clinical trials. Biomed. Pharmacother. 37, 14-24, 1983.

160. TRAVADE P., CHASTANG C., AUGUIER A., DIGHIERO G., PIGUET H., LEBLAY M., POTRON G., COLONA P., LEPORRIER M., GOASGUEN J., OBERLING F., TCHERNIA G., BOIVIN P., JACQUILAT C., BRIERE J., TURPIN F. and BINET J. L.: Resultats préliminaires du protocole LLC 76, in BERNARD A., BOUMSELL L. and DEMEOCQ F. (eds): Biologie des Leucémies et Hématosarcomes. Paris, G. Lachurié, 1983.

161. SALMON S. E., ALEXANIAN R. and DIXON D.: Chemoimmunotherapy for

multiple myeloma. Effect of levamisole during maintenance, in TERRY W. D. and ROSENBERG S. A. (eds): Immunotherapy of Human Cancer, p. 61. New York, Excerpta Medica, 1982.

162. HOERNI B., DURAND M., EGHBALI H., HOERNI-SIMON G. and LAGARDE C.: Adjuvant BCG-therapy of non-Hodgkin's malignant lymphomas, in SALMON S. E. and JONES S. E. (eds): Adjuvant Therapy of Cancer III, p. 99. New York, Grune & Stratton, 1981.

163. JONES S. E.: Chemoimmunotherapy of malignant lymphoma, in TERRY W. D. and ROSENBERG S. A. (eds): Immunotherapy of Human Cancer, p. 55. New York, Excerpta Medica, 1982.

164. JONES S. E., SALMON S. E. and FISHER R.: Adjuvant immunotherapy with BCG in non-Hodgkin's lymphoma: a Southwest Oncology Group Controlled Clinical Trial, in JONES S. E. and SALMON S. E. (eds): Adjuvant Therapy of Cancer II, p. 163. New York, Grune & Stratton, 1979.

165. REIZENSTEIN P., ANDERSSON B., BJORKHOLM M., BRENNING G., ENGSTEDT L., GAHRTON G., HAST R., HOLM G., HORNSTEN P., KILLANDER A., LANTZ B., LINDEMALM C., LOCKNER D., LONNQVIST B., MELLSTEDT H., PALMBLAD J., PAUL C., SIMONSSON B., SJOGREN A. M., STALFELT A. M., UDEN A. M., WADMAN B., OBERG G. and OSBY E.: BCG plus leukemic cell therapy in patients with acute nonlymphoblastic leukemia: effect in groups with high and low remission rates, in TERRY W. D. and ROSENBERG S. A. (eds): Immunotherapy of Human Cancer, p. 17. New York, Excerpta Medica, 1982.

166. BEKESI J. G. and HOLLAND J. F.: Therapeutic effectiveness of neuraminidase-treated allogeneic myeloblasts as immunogen in acute myelocytic leukemia, in MATHÉ G., BONADONNA G. and SALMON S. (eds): Adjuvant Therapies of Cancer, p. 42. Berlin, Springer, 1982.

167. OTA K.: A phase III study of bestatine as adjuvant immunotherapy of acute myeloid leukemia, in MATHÉ G. and UMEZAWA H. (eds): Antibiotics in Cancer Treatment. Tokyo, Trends in Antibiotic Research, in press.

168. SCHWARZENBERG L. & MATHÉ G.: The visual expression of comparative trial results (remission compared to mortality, the one patient plateau), in MATHÉ G., REIZENSTEIN P. and DICATO M. (eds): Therapeutical Trials in Oncology: Methods, Ethics, Results. Geneva, Bioscience Ediprint, in press.

169. EILBER F. R., MORTON D. L., HOLMES E. C., SPARKS F. C. and RAMMING K. P.: Adjuvant immunotherapy with BCG in treatment of regional lymph node metastases from malignant melanoma. New Engl. J. Med. 294, 237, 1976.

170. MORTON D. L., CARMACK HOLMES E., EILBER F. R. and RAMMING K. P.: Adjuvant immunotherapy of malignant melanoma: results of a randomized trial in patients with lymph node metastases, in TERRY W. D. and ROSENBERG S. A. (eds): Immunotherapy of Human Cancer, p. 245. New York, Excerpta Medica, 1982.

171. SPITLER L. E. and SAGEBIEL R.: A randomized trial of levamisole versus placebo as adjuvant therapy in malignant melanoma. New Engl. J. Med. 303, 1143, 1980.

172. OKA T.: Bestatin as melanoma adjuvant therapy, in MATHÉ G. and UMEZAWA H. (eds): Antibiotics in Cancer Treatment. Tokyo, Trends in Antibiotics Research, in press.

173. STRANDER H., APARISI T., BLOMGREN H., BROSTROM L. A., CANTELL K., EINHORN S., INGIRMASSON S., NILSONNE U. and SODERBERG G.: Adjuvant interferon treatment of human osteosarcoma, in MATHÉ G., BONADONNA G. and SALMON S. (eds): Adjuvant Therapies of Cancer, p. 103. Berlin, Springer, 1982.

174. GEROSA M. A., OLIVI A., ROSENBLUM M. L., SEMENZATO G. P. and PEZZUTTO A.: Impaired immunocompetence in patients with malignant gliomas: the possible role of Tg-lymphocyte subpopulations. Neurosurgery 10, 571, 1982.

175. MAVER C., KAUSEL H., LININGER G. and MCKNEALLY M.: Intrapleural BCG immunotherapy of lung cancer patients, in MATHÉ G., BONADONNA G. and SALMON S. (eds): Adjuvant Therapies of Cancer, p. 227. Berlin, Springer, 1982.

176. YASUMOTO K. and YAMAMURA Y.: Randomized clinical trial of non specific immunotherapy with cell-wall skeleton of Nocardia rubra. Biomed. Pharmacother. 38, 48-54, 1984.

177. STEWART T. H. M., HOLLINSHEAD A. C., HARRIS J. E. and RAMAN S.: Specific active immunotherapy in lung cancer: the induction of long-lasting cellular responses to tumour associated antigens, in MATHÉ G., BONADONNA G. and SALMON S. (eds): Adjuvant Therapies of Cancer. Berlin, Springer, 1982.

178. FOCAN C., FOCAN-HENRARD D., SCHYNS-MOSEN J., FRERE M. H., HALEN M. and LEHUNG S.: Levamisole (L) versus placebo (O) for prolongation of remission and survival in human solid tumors. A double-blind randomized trial, in 10th Congress of the European Society for Medical Oncology, Nice 7–9 Dec. 1984.

179. OCHIAI T.: Gastric tumors: immunotherapy, in MATHÉ G., REIZENTSTEIN P. and DICATO M. (eds): Therapeutical Trials in Oncology: Methods, Ethics, Results. Geneva, Bioscience Ediprint, in press.

180. ROBINSON E.: Colorectal tumors: immunotherapy, in MATHÉ G., REIZENSTEIN P. and DICATO M. (eds): Therapeutical Trials in Oncology: Methods, Ethics, Results. Geneva, Bioscience Ediprint, in press.

181. CAMACHO F., PINSKY C., KERR D., WHITMORE W. and OETTGEN H.: Treatment of superficial bladder cancer with intra-vesical BCG, in Proc. Int. Conf. Immunother. Cancer, Bethesda, 28–30 April, 1980.

182. ALBERTS D., MOONN T., O'TOOLE R., NEFF J., TATE THIGPEN J. and BLESSING J.: BCG as an adjuvant to adriamycin-cyclophosphamide in the treatment of advanced ovarian carcinoma: ongoing analysis of a Southwest Oncology Study Group, in JONES S. E. and SALMON S. (eds): Adjuvant Therapy of Cancer II, p. 1653. New York, Grune & Stratton, 1979.

183. LACOUR J., LACOUR F., SPIRA A., MICHELSON M., PETIT J. Y., DELAGE G., SARRAZIN D., CONTESSO G. and VIGUIER J.: Adjuvant treatment with polyadenylic–polyuridylic acid (poly-A–polyU) in operable breast cancer. Lancet 2, 161, 1980.

184. LACOUR J., LACOUR F., SPIRA A., MICHELSON M., PETIT J. Y., DELAGE G., SARRAZIN D., CONTESSO G. and VIGUIER J.: Adjuvant treatment with polyadenylic–polyuridylic acid in operable breast cancer: updated results of a randomized trial. Br. Med. J. 288, 589-592, 1984.

185. MATHÉ G.: Absence of late relapse(s) in the active immunotherapy treated acute lymphoid leukemia patients. Comparison with their incidence and types after chemotherapy. In preparation.

186. LAND V. J., BERRY D. H., HERSON J., MIALE T., RIED H., SILVA-SOSA M. and STARLING K.: Long-term survival in childhood acute leukemia 'late' relapses. Med. Ped. Oncol. 7, 19-24, 1979.

187. BAUM E., SATHER H., NACHMAN J., SEINFELD J., KRIVIT W., LEIKIN S., MILLER D., JOO P. and HAMMOND D.: Relapse rates following cessation of chemotherapy during complete remission of acute lymphocytic leukemia. Med. Ped. Oncol. 7, 25-34, 1979.

188. MATHÉ G., AMIEL J. L. and SCHWARZENBERG L.: Bone Marrow Transplantation and Leucocyte Transfusions. Springfield IL, C. C. Thomas, 1971.

189. MATHÉ G., AMIEL J. L. and NIEMETZ J.: Greffe de moelle osseuse après irradiation totale chez des souris leucémiques, suivie de l'administration d'un antimitotique pour réduire la fréquence du syndrome secondaire et ajouter à l'effet antileucémique. C. R. Acad. Sci., Paris 254, 3602, 1962.

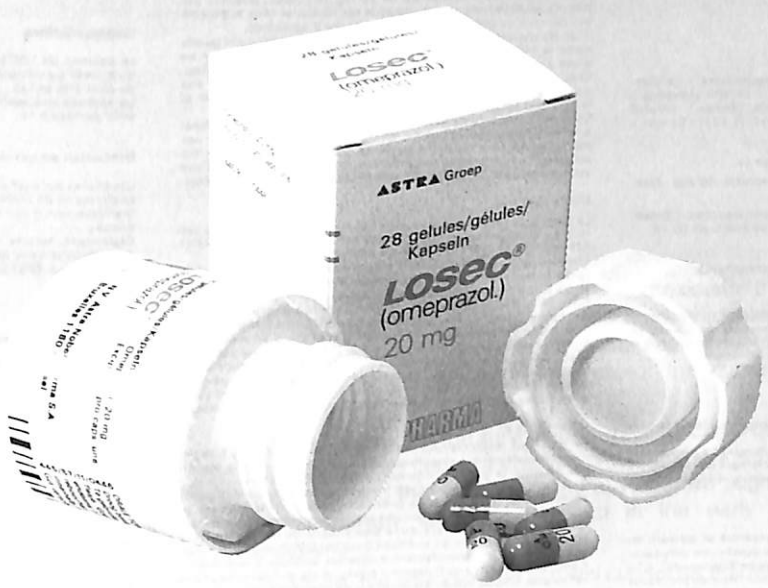
190. MATHÉ G. and AMIEL J. L.: Réduction de la concentration plasmatique du virus leucémigène de Charlotte Friend par immunothérapie adoptive (greffe de moelle osseuse allogénique). C. R. Acad. Sci., Paris 259, 4408, 1964.

191. WEIDEN P. L., FLOURNOY N., THOMAS E. D., PRENTICE R., FEFER A., BUCKNER C. D. and STORB R.: Antileukemic effect of graft-versus-host disease in human recipients of allogeneic-marrow grafts. New Engl. J. Med. 300, 1068, 1979.

192. GALE R. P. and CHAMPLIN R. E.: How does bone-marrow transplantation cure leukaemia? Lancet 2, 28-30, 1984.

193. FISHER B.: Combined modality treatment of cancer, pp. 1/99-1/108 in Main Lectures 1–10, pp. 1/99-1/108, 13th Internat. Congress of Chemotherapy, Vienna 28 August–2 September 1984.

Losec®



Ulcère Duodénal			2 sem.
Ulcère Gastrique	20	par jour	4 sem.
Oesophagite par Reflux			
Ulcère réfractaire	20 20	par jour à jeun	4 à 8 sem.

N.V. ASTRA-NOBELPHARMA S.A.

Dénomination

LOSEC®

(oméprazole)

Titulaire d'enregistrement

N.V. ASTRA-NOBELPHARMA S.A.
1180 BRUXELLES

Fabricant

ASTRA (Suède)

Composition

LOSEC®, gélules à 20 mg

Omeprazol. 20 mg - Mannitol - Hydroxypropylcellulos. - Cellulos. microcrist. - Natr. laurylsulfas - Lactosum - Dinatrii phosphas - Hypromellos. - Hydropropylmethyl - cellulos. phtalas. - Alcohol cetyl. - Ferr. oxyd. rubr. (E 172) - Titan. dioxyd. (E 171) - Gelatin. - Enc. q.s. pro capsula una.

LOSEC®, poudre injectable pour administration i.v.

Vial : Natr. omeprazol. 42,6 mg = Omeprazol. 40 mg - Natr. hydroxyd q.s. ad pH 12.

Ampoule : Macrogol 400 - Natr. dihydrogenophosphas - Dinatr. phosphas q.s. ad pH 7,5 - Aqua ad iniect. ad 10 ml.

Formes, voies d'administration et conditionnements

- LOSEC®, gélules à 20 mg : 28 gélules.
- LOSEC®, poudre injectable pour administration i.v. : boîte de 1 vial contenant l'oméprazole lyophilisé et 1 ampoule de solvant. La solution pour injection intraveineuse est obtenue en dissolvant l'oméprazole lyophilisé avec le solvant de l'ampoule.

Propriétés

LOSEC (oméprazole) réduit la sécrétion gastrique acide grâce à un mécanisme d'action entièrement nouveau.
L'oméprazole est un inhibiteur spécifique de la pompe à proton gastrique dans la cellule pariétale. L'oméprazole agit rapidement ; il exerce un contrôle réversible de la sécrétion gastrique acide avec une seule administration quotidienne.

Lieu et mécanisme d'action :

L'oméprazole est une base faible. Il est concentré et converti en forme active dans l'environnement acide des canalicules intracellulaires au sein de la cellule pariétale, où il inhibe l'enzyme H^+, K^+ - ATPase - la pompe à proton. Cet effet sur l'étape finale du processus de formation de l'acide gastrique dépend de la dose et entraîne une inhibition efficace, à la fois de la sécrétion acide basale et de la sécrétion acide stimulée, quel que soit le sécrétagogue.
L'oméprazole n'a pas d'effet sur les récepteurs de l'acétylcholine ou de l'histamine. On n'a pas observé d'effets pharmacodynamiques, cliniquement significatifs, étrangers à ceux qui s'expliquent par l'action de l'oméprazole sur la sécretion acide.

Effet sur la sécrétion acide :

L'administration orale de LOSEC, à raison de 20 mg une fois par jour, entraîne une inhibition rapide et efficace de la sécrétion acide de l'estomac. L'effet maximum du traitement est atteint dans les 4 jours. Chez les patients souffrant d'ulcère duodénal, une diminution moyenne de 80 % environ de l'acidité intragastrique sur 24 heures est alors maintenue, tandis que la diminution moyenne du pic du débit acide après stimulation par la pentagastrine est d'environ 70 %, 24 heures après l'administration de LOSEC.

Absorption et distribution :

L'oméprazole est labile en milieu acide. Il est administré par voie orale sous forme de granules à enrobage entérique, contenus dans une gélule.
L'absorption se produit dans l'intestin grêle ; elle est généralement complète en 3-6 heures. La biodisponibilité systémique de l'oméprazole, à partir d'une dose orale unique de LOSEC, est d'environ 35 %. Après administration répétée d'une dose quotidienne, la biodisponibilité augmente jusqu'à 60 % environ. L'absorption simultanée de nourriture n'a pas d'influence sur la biodisponibilité. La liaison de l'oméprazole aux protéines plasmatiques est d'environ 95 %.

Elimination et métabolisme :

La demi-vie moyenne de la phase terminale de la courbe des concentrations plasmatiques par rapport au temps est approximativement de 40 minutes. La demi-vie ne change pas au cours du traitement. L'inhibition de la sécrétion acide est en relation avec la surface sous la courbe, mais non avec la concentration plasmatique présente à un moment donné.
L'oméprazole est entièrement métabolisé, principalement dans le foie. Les métabolites identifiés dans le plasma sont le dérivé sulfoné, le dérivé sulfuré et l'hydroxy-oméprazole, ces métabolites n'exerçant pas d'effet significatif sur la sécrétion acide. Environ 80 % des métabolites sont excrétés dans l'urine et le restant, dans les fèces. Les deux principaux métabolites urinaires sont l'hydroxy-oméprazole et l'acide carboxylique correspondant.
La biodisponibilité systémique de l'oméprazole n'est pas altérée de façon significative chez les patients ayant une fonction rénale réduite. La surface sous la courbe des concentrations plasmatiques par rapport au temps est augmentée chez les patients ayant une fonction hépatique altérée, mais l'on n'a pas trouvé de tendance à une accumulation de l'oméprazole.

Indications

LOSEC est indiqué pour le traitement de :

- l'ulcère duodénal
- l'ulcère gastrique
- l'oesophagite de reflux
- le syndrome de Zollinger-Ellison.

Posologie et mode d'emploi

ADMINISTRATION ORALE

Ulcère duodénal

La posologie recommandée est de 20 mg de LOSEC, une fois par jour. Le soulagement symptomatique est rapide et chez la plupart des patients, la guérison intervient endéans 2 semaines.
Chez les patients qui pourraient n'avoir pas été entièrement guéris après le traitement initial, la guérison s'obtient généralement au cours d'une période de traitement supplémentaire de 2 semaines.
Chez les patients porteurs d'un ulcère duodénal réfractaire aux autres traitements, on a utilisé 40 mg de LOSEC une fois par jour, et la guérison est généralement intervenue endéans 4 semaines.
Comme l'expérience du traitement à long terme de l'ulcère duodénal avec LOSEC est encore limitée, un traitement d'entretien n'est pas recommandé tant qu'une expérience plus large n'aura pas été acquise. Pour éviter rechute ou récidive, on aura donc recours à une autre thérapeutique, à déterminer individuellement selon le patient.

Ulcère gastrique

La posologie recommandée est de 20 mg de LOSEC, une fois par jour. Le soulagement symptomatique est rapide et chez la plupart des patients, la guérison intervient endéans 4 semaines.
Chez les patients qui pourraient n'avoir pas été entièrement guéris après le traitement initial, la guérison s'obtient généralement au cours d'une période de traitement supplémentaire de 4 semaines.
Chez les patients porteurs d'un ulcère gastrique réfractaire aux autres traitements, on a utilisé 40 mg de LOSEC une fois par jour, et la guérison est généralement intervenue endéans 8 semaines.
Comme l'expérience du traitement à long terme de l'ulcère gastrique avec LOSEC est encore limitée, un traitement d'entretien n'est pas recommandé tant qu'une expérience plus large n'aura pas été acquise. Pour éviter rechute ou récidive, on aura donc recours à une autre thérapeutique, à déterminer individuellement selon le patient.

Oesophagite de reflux

La posologie recommandée est de 20 mg de LOSEC, une fois par jour. Le soulagement symptomatique est rapide et chez la plupart des patients, la guérison intervient endéans 4 semaines.
Chez les patients qui pourraient n'avoir pas été entièrement guéris après le traitement initial, la guérison s'obtient généralement au cours d'une période de traitement supplémentaire de 4 semaines.
Chez les patients souffrant d'une oesophagite de reflux réfractaire aux autres traitements, on a utilisé 40 mg de LOSEC une fois par jour, et la guérison est généralement intervenue endéans 8 semaines.
Comme l'expérience du traitement à long terme de l'oesophagite de reflux avec LOSEC est encore limitée, un traitement d'entretien n'est pas recommandé tant qu'une expérience plus large n'aura pas été acquise. Pour éviter rechute ou récidive, on aura donc recours à une autre thérapeutique, à déterminer individuellement selon le patient.

Syndrome de Zollinger-Ellison

La posologie initiale recommandée est de 60 mg de LOSEC par jour. La posologie doit être ajustée individuellement et le traitement poursuivi aussi longtemps qu'il est indiqué d'un point de vue clinique. Tous les patients gravement atteints et ne répondant pas de façon adéquate à d'autres thérapeutiques, ont été contrôlés efficacement et plus de 90 % des patients ont été maintenus à des doses de 20-120 mg par jour. Pour les posologies supérieures à 80 mg par jour, la dose quotidienne doit être répartie en deux prises.

Posologie en cas d'altération de la fonction rénale et hépatique

Il n'est pas nécessaire d'effectuer un ajustement de la posologie chez les patients souffrant d'une altération de la fonction rénale ou hépatique.

ADMINISTRATION INTRAVEINEUSE

Lorsqu'une thérapeutique orale est inadéquate, p.ex. chez des patients gravement malades, on recommande l'administration intraveineuse de LOSEC, à raison de 40 mg par jour. Ce traitement entraîne une diminution immédiate de l'acidité intragastrique, avec une diminution moyenne sur 24 heures d'environ 90 %.
Dans le syndrome de Zollinger-Ellison, la posologie doit être ajustée individuellement, et une posologie plus élevée avec une administration plus fréquente peut s'avérer nécessaire.
La solution i.v. est obtenue par dissolution de l'oméprazole lyophilisé à l'aide du solvant contenu dans l'ampoule (il ne faut pas utiliser d'autre solvant).La solution de LOSEC ainsi reconstituée doit être utilisée uniquement pour l'injection i.v. et ne peut pas être ajoutée à des solutions pour perfusion i.v.
Après reconstitution, la solution doit être injectée lentement sur une période d'au moins 2 1/2 minutes et à une vitesse maximum de 4 ml par minute.
La solution doit être utilisée endéans les 4 heures après sa reconstitution.

ENFANTS

On ne dispose pas d'une expérience clinique avec LOSEC chez l'enfant.

PATIENTS AGES

Il n'est pas nécessaire d'effectuer un ajustement de la posologie chez les patients âgés.

Contre-indications

Il n'existe pas de contre-indications connues à l'utilisation de LOSEC.

Effets indésirables

LOSEC est bien toléré. On a signalé des nausées, des maux de tête, de la diarrhée, de la constipation et de la flatulence mais ces cas ont été rares.
Chez quelques patients, on a observé une éruption cutanée. Ces effets indésirables ont été généralement dépourvus de gravité et transitoires, et leur relation avec le traitement n'a pas été uniforme.

Précautions particulières

Si l'on suspecte un ulcère gastrique, la possibilité de malignité doit être préalablement exclue, car le traitement peut atténuer les symptômes et retarder le diagnostic.

Incompatibilités

La solution de LOSEC pour injection i.v. ne peut être reconstituée qu'à partir du solvant contenu dans l'ampoule. Aucun autre solvant ne peut être utilisé.
La solution reconstituée ne peut pas être ajoutée à des solutions pour perfusion i.v.

Utilisation en cas de grossesse et de lactation

Les études sur animaux n'ont mis en évidence aucun risque lié à l'administration de LOSEC durant la gestation et la lactation et aucune manifestation d'une toxicité foetale ou d'un effet tératogène n'a été relevée.
Cependant, comme tout nouveau médicament, LOSEC ne devrait être administré pendant la grossesse et la lactation que si son utilisation est considérée comme indispensable.

Interactions

LOSEC peut prolonger l'élimination du diazépam et de la phénytoïne, substances qui sont métabolisées par oxydation dans le foie. Il est donc recommandé de surveiller les patients qui reçoivent de la phénytoïne, une réduction de la dose de phénytoïne pouvant être nécessaire. On n'a pas trouvé d'interaction avec la théophylline, mais il pourrait y avoir des interactions avec d'autres médicaments métabolisés par l'intermédiaire du système enzymatique du cytochrome P 450, comme la warfarine.
On n'a pas trouvé d'interaction avec les antacides administrés conjointement.

Surdosage

On ne dispose pas d'information sur les effets d'un surdosage chez l'homme et il n'est donc pas possible de donner des recommandations spécifiques pour un traitement.

Des doses orales uniques allant jusqu'à 160 mg et des doses intraveineuses uniques allant jusqu'à 80 mg ont été bien tolérées. Des doses intraveineuses allant jusqu'à 200 mg en un seul jour et jusqu'à 520 mg sur une période de trois jours ont été administrées sans effets indésirables.

Conservation

LOSEC®, gélules à 20 mg : conservation à température ambiante (15°-25°) et à l'abri de l'humidité.

LOSEC®, poudre injectable pour administration i.v. : conservation au réfrigérateur (2°-8°) et à l'abri de la lumière.
La solution reconstituée est stable pendant 4 heures à température ambiante (15°-25°).

Stabilité :

Une date de péremption figure sur l'emballage : EX signifiant expiration suivi de 4 chiffres, les deux premiers indiquant le mois (1 ^{er} jour) et les deux derniers l'année.

Délivrance

Sur prescription médicale.

Dernière mise à jour de la notice

Implications of Survival Curve Slopes on the Interpretation of Adjuvant Therapy Results

M. Eriguchi and G. Mathé

Abstract

Two mathematical models can approximate the survival curves for malignant diseases. The models identify the segments of the survival curve. Also, the hazard function of the curve and the confidence intervals of the curve could be calculated.

First, we studied the survival-after-relapse curve of malignant melanoma. The curve of chemo-immunotherapy showed three segments and that for immunotherapy had two segments. The immunotherapy showed its effect in the early period of treatment.

Second, the disease-free survival curves for adjuvant therapies of breast cancer were compared. In the Oncofrance trial, a combination of adriamycine, vincristine, cyclophosphamide (C) and 5-fluoro-uracil (F) (AVCF) was superior to a combination of C, methotrexate and F (CMF) in all the periods of the therapy. In Lacour's trial, poly A–poly U was more effective than the no treatment in the middle and late period. In Bonadonna's trial, CMF was superior to no treatment in the early period.

Third, the survival curves for immunotherapy versus non-immunotherapy of stomach cancer were analysed. Comparison of the confidence intervals of each curve clarified that no significant difference could be found between them.

INTRODUCTION

There are three kinds of survival curves: those describing the duration of remission or of disease-free survival (DFS), those describing overall survival and those describing survival after relapse. These curves have several segments or sub-populations. Morton (9) has described the survival curve of patients with malignant melanoma as having three sub-populations: those who relapse or die soon, those who relapse or die late and those who neither relapse nor die, and who may be considered as cured.

Department of Surgery, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-Ku, Tokyo, Japan

Department des Maladies Sanguines et Tumorales et I.C.I.G., Université Paris-Sud, CNRS VA 04-1163, Hôpital Paul-Brousse, 94804-Villejuif, France

Theoretical models suggest two types of survival curves, a convex–concave curve and a concave curve (Fig. 1) (11). To describe these curves, the Weibull, log-normal and exponential distributions have been used (1,3,12).

The theoretical models proposed here can be used to identify slopes of curve segments and to calculate the hazard function (3) and the confidence intervals of the curve. The results of adjuvant therapies for malignant melanoma, breast cancer and stomach cancer are thus analysed.

MATERIALS AND METHODS

S(t) was defined as the probability of survival at time t. Figure 1 shows the equation for the concave and the convex–concave curves, respectively. Observed data were used to obtain the equation by the least squares method. Among the several equations which could be obtained for one given curve, the one having the smallest residual variance was selected. It was possible to identify several segments in the curve (Fig. 2), the number of observations or patients, and the slope or mortality or relapse rate of each segment. If the curve was composed of three segments, these segments were assumed to reflect, respectively, the high risk, intermediate risk and low risk groups.

Linearity is necessary for obtaining the constant death rate or relapse rate of the segments.

Relapse rates could not be compared in all trials because the curves of some segments were not linear on a semi-log scale. Therefore the hazard functions were compared. The hazard function, which is correlated with the slope of the curve and its confidence intervals, was then calculated.

The Oncofrance trial of adjuvant therapy for melanoma (6), in which the survival-after-relapse curve of the immunotherapy group was compared to that of chemo-immunotherapy, was analysed with this method.

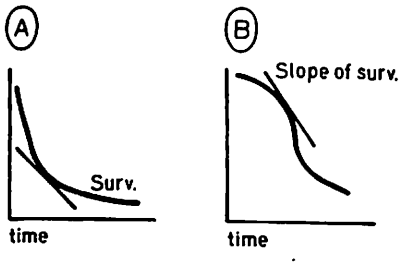


Fig. 1. Two theoretical models of survival curve on a semi-log scale. Equation (A): the probability of the survival stands for a concave curve and equation (B): the probability of the survival for a convex–concave curve. The tangential line of the curve represents the slope of curve.

$$\text{Equation (A): } P(t) = \sum_{i=1}^{3} \text{Exp}(-\lambda i t + Ni).$$

$$\text{Equation (B): } P(t) = \sum_{i=1}^{2} \text{Exp}(-\lambda i t + Ni) + \text{Exp}\left[\sum_{i=3}^{4} -\lambda i t^{2(i-2)} + N^3\right].$$

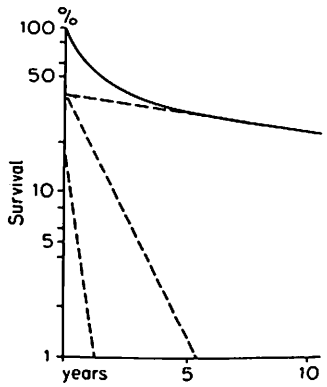


Fig. 2. A hypothetical concave survival curve on semi-log scale. The original curve is the addition of three curves (in dotted lines) which are suggested to represent the high risk, intermediate risk and low risk groups, respectively.

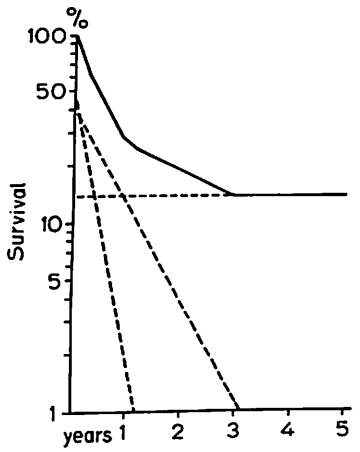


Fig. 3. Observed survival curve after relapse in melanoma according to adjuvant treatment: chemo-immunotherapy (solid line). It is composed of three segments (dotted lines).

In addition, three trials of adjuvant therapy for breast cancer, the Oncofrance trial (7), Lacour's trial (4) and Bonadonna's trial (10) were studied. The Oncofrance trial compared a combination of cyclophosphamide, methotrexate and 5-fluoro-uracil (CMF) with a combination of adriamycin, vincristine, cyclophosphamide and 5-fluoro-uracil (AVCF). The disease-free survival curve for pre-menopausal patients with positive nodes (N+) was analysed both in the Oncofrance and in Lacour's trials, where poly A-poly U treatment was compared to no treatment. In Bonadonna's trial, cyclophosphamide, methotrexate and 5-fluoro-uracil (CMF) was compared to no treatment, and the disease-free survival curve for pre-menopausal patients was analysed. Finally, Fujii's trial (2,8) of adjuvant immunotherapy for stomach cancer was analysed.

RESULTS

Melanoma

Figure 3 shows the analysed curves of melanoma. The equations of the curves were as follows: chemo-immunotherapy: $S(t) = \exp(-3.246t + 3.813) + \exp(-1.173t + 3.706) + \exp(0t + 2.639)$. Three segments could thus be identified. Immunotherapy: $S(t) = \exp(-1.196t + 4.435) + \exp(-0.035t + 3.150)$. Two segments were identified. It is suggested here that immunotherapy 'shifts' the high risk group of chemo-immunotherapy into the intermediate risk group.

Breast cancer

The following equation was formed for breast cancer treated with CMF in the Oncofrance trial: $S(t) = \exp(-0.205t^2\ 0.0007t^4 + 3.929) + \exp(°t + 3.911)$, i.e. two segments. AVCF in the Oncofrance trial: $S(t) = \exp(-0.064t^2 - 0.040t^4 + 2.870) + \exp(0t + 4.414)$, also two segments. It is suggested here that 30% of the patients were 'shifted' by AVCF from the high risk group of CMF to the low risk group.

Lacour's controls: $S(t) = \exp(-0.198^2t + 4.224) + \exp(-0.082t + 3.474)$, again two segments. Poly A-poly U of Lacour's trial: $S(t) = \exp(-0.372t^2 + 2.818) + \exp(-0.036t + 4.428)$, two segments. Half of the controls at high risk seem to have been 'shifted' to the low risk group by poly A-poly U.

The controls in Bonadonna's trial (Fig. 4): $S(t) = (-0.883t + 3.473) + \exp(-0.511t + 3.322) + \exp(0t + 3.689)$, i.e. three segments.

CMF in Bonadonna's trial: $S(t) = \exp(-0.347t^2 + 2.715) + \exp(-0.054t + 4.437)$, two segments. The CMF treatment seems to have 'shifted' half of the controls in the high risk group and all in the intermediate risk group.

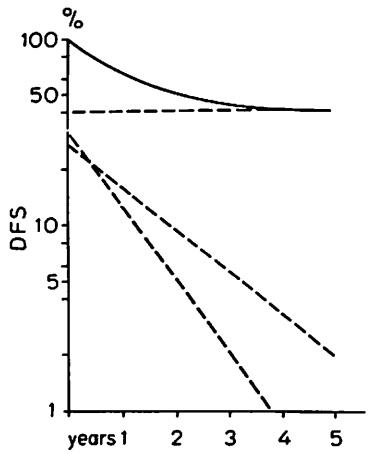


Fig. 4. Observed disease-free survival curve of the control group in adjuvant therapy of breast cancer (premenopausal) in Milan (solid line). It has three segments (dotted lines).

The hazard function of the Oncofrance AVCF suggests that AVCF is better than the Oncofrance CMF in all the periods.

The result of Lacour's poly A-poly U treatment was superior only in the middle and late periods. In contrast, the result of Bonadonna's CMF treatment was superior in the early period.

Figures 5 and 6 show the analysis of the survival curves of stomach cancer in different stages. The equation for patients given immunotherapy was: $S(t) = \exp(-0.324t^2 + 3.088) + \exp(-0.024t + 4.366)$. That for no immunotherapy was: $S(t) = \exp(-0.624t^2 + 3.207) + \exp(-0.008t + 4.282)$. Each curve has two segments. The 95% confidence intervals of the curves show that results of immunotherapy are superior only in the short early period.

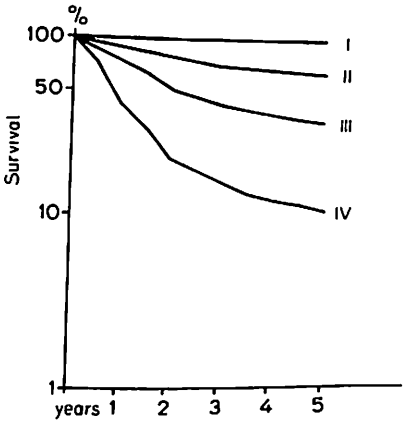


Fig. 5. Observed survival curves of patients with gastric cancer in Japan according to stage.

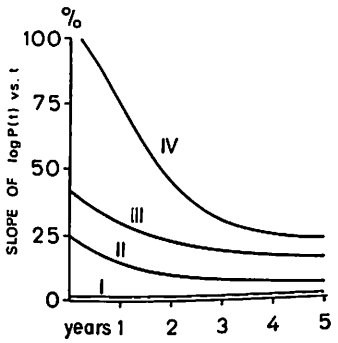


Fig. 6. Slopes of survival curves of patients with gastric cancer in Japan according to stage.

DISCUSSION

A comparison of the hazard functions, which can be calculated from the equation of each curve, can indicate during which period the adjuvant treatment is effective.

Mathé (5) has suggested that adjuvant chemotherapy works on the first segment

assumed to represent the high risk group and adjuvant immunotherapy on the second segment, the intermediate risk group. This could suggest that chemotherapy affects many tumor cells in cycle and that immunotherapy affects tumor cells in G_0.

Acknowledgements

The authors thank Dr Y. Eriguchi, Department of Earth Science and Astronomy, College of Arts and Science, University of Tokyo, Japan, for the programming and computation.

REFERENCES

1. BOAG J. W.: Maximum likelihood estimates of the proportion of the patients cured by cancer therapy. J. Roy. Stat. Soc. B11, 15, 1949.
2. FUJII G.: Cancer immunology and immunotherapy. Shōkakigeka Sem. 16, 67, 1984.
3. GROSS A. J. and CLARK V. A.: Survival Distributions: Reliability Applications in Biomedical Science. New York, John Wiley, 1975.
4. LACOUR J., LACOUR F., SPIRA A., MICHELSON M., PETIT J. Y., DELAGE G., SARRAZIN D., CONTESSO G. and VIGUIER J.: Adjuvant treatment with polyadenylic-polyuridylic acid (poly A–poly U) in operable breast cancer. Lancet ii, 161, 1980.
5. MATHÉ G., ERIGUCHI M. and REIZENSTEIN P.: Cancer Residual Disease and its Adjuvant Chemotherapy and Immunotherapy. Do we Cure Cancer? Amsterdam, Elsevier, in press.
6. MISSET J. L., DELGADO M., MATHÉ G., SERROU B., CUPISSOL D., JEANNE C., CHEVRIER A., GUERRIN J., FARGEOT P., PLAGNE R., CHOLLET P., SCHNEIDER M., LE MEVEL B., FUMOLEAU P., MORICE V. and GAGET H.: Eight-year update of the Oncofrance Melanoma Adjuvant Trial, in JONES S. E. and SALMON S. E. (eds): Adjuvant Therapy of Cancer IV, p. 557. New York, Grune & Stratton, 1986.
7. MISSET J. L., DELGADO M., DE VASSAL F., HAYAY M., JASMIN C., MACHOVER D., MUSSET M., RIBAUD P., SCHWARZENBERG L., MATHÉ G., BELPOMME D., CHOLLET P., PLAGNE R., METZ R., LE MEVEL B., FUMOLEAU P., GUERRIN J., FARGEOT D., JEANNE C., SCHNEIDER M., MORICE V. and GAGET H.: Five-year results of the French adjuvant trial for breast cancer comparing CMF to a combination of Adriamycin (ADM), Vincristine (VCR), Cyclophosphamide (CPM), and 5-Fluorouracil (5FU), in JONES S. E. and SALMON S. E. (eds): Adjuvant Therapy of Cancer IV, p. 243. New York, Grune & Stratton, 1986.
8. MIYAMOTO Y., FUJII G., SEKIGUCHI M., SAMARU Y., KOISHI T., MIKAMO S., HAGIWARA T., TAKAHASHI T., FUJII Y. and TAKEDA Y.: Factors influencing the effect of postoperative adjuvant treatment for stomach cancer, in: 85th Annual Meeting of Japan Surgical Society, Sendai, Japan, 3–5 April 1985.
9. MORTON D., GUPTA R. K. and HUTH J. F.: New horizons in surgical oncology: malignant melanoma, in TORISU M. and YOSHIDA T. (eds): Basic Mechanisms and Clinical Treatment of Tumor Metastasis, p. 562. Tokyo, Academic Press, 1985.
10. ROSSI A., BONADONNA G., VALAGUSSA P. and VERONESI U.: Multimodal treatment in operable breast cancer: five-year results of CMF programme. Br. Med. J. 282, 1427, 1981.
11. SHACKNEY S. E., MCCORMACK G. W. and CUCHURAL G. J. Jr: Growth rate patterns of solid tumor and their relation to responsiveness to therapy. Ann. intern. Med. 89, 107, 1978.
12. WEIBULL W.: A statistical distribution of wide applicability. J. appl. Mech. 18, 293, 1951.

Ethical Problems in Clinical Trials Concerning Minimal Residual Tumors*

Sophie Dion and Peter Reizenstein

INTRODUCTION

The treatment effectiveness of imperceptible tumors is judged by the duration of remission and/or survival. Since these patients are usually apparently healthy and free from symptoms, and may in fact even be cured already, particular care is required from an ethical and legal stand-point.

PHASE II TRIALS

Relatively few basic ethical problems present themselves in the comparative or prolonged phase II trials. It is an ethical advantage if the oriented phase II trial according to Gehan's rigorous statistical design is used which requires only 25 patients to detect a 20% difference in treatment effect with a $p<0.05$ (1,2). In this way, the need of a very large patient population to obtain statistical significance and the inclusion of too many subjects might be avoided.

If there is a heterogeneous distribution of patients within the groups, a requirement of 3000 patients in order to detect a 20% difference has been considered necessary (15). Even larger numbers of patients are sometimes subjected to trials in order to affirm that smaller differences are statistically significant. Such figures are both ethically and pragmatically questionable. It is important to balance the risk against the importance of calculating the significance of a small difference.

*For the Committee on Ethics. Members: Dr P. Bailly; Rabbin Bernheim; Pr J. P. Bouvier; Mrs D. Bruneval (student); Archbishop J. B. Brunon; Dr B. Ceoara (primary health care); Mr J. Crozemarie (President of the Association pour la Recherche contre le Cancer); Prof. G. Durry (Faculty of Law); G. Henry, Archbishop, Athens (French League against Cancer); Mrs A. Le Troquer; Pr E. Lisle (statistician); Mrs G. Pallez; Dr P. Reizenstein; Mr G. Uzan (judge); Dr E. Yamasaki; A. Zurini (lawyer).

Attorney-at-law, Appelate Court, Paris and Service des Maladies Sanguines et Tumorales, Hôpital Paul-Brousse, 94804-Villejulf, France

Division of Hematology, Karolinska Hospital, S-10401 Stockholm, Sweden

PATIENTS AT RISK

Every patient in a clinical trial is at risk and the physician is responsible. In the U.S., every death during a clinical trial involving new drugs must be reported within 24 hours to the authorities, even if death was not related to the trial. Every protocol thus includes a risk, related to the rigidity of the protocol and to the fact that, for instance, dose corrections for individual variations of pharmacokinetics are not always anticipated and are sometimes even prohibited. In a trial in Memphis (3), nine children developed leuco-encephalopathy, and in the polycythemia vera study group, a large number of acute leukemias were induced before the treatment was stopped. This is ethically and legally unacceptable. Individualized treatment may well entail advantages, both as regards economy and patient satisfaction, in comparison to the rigid protocol required for randomized trials (4). Protocols should thus attempt to provide for planned, standardized individualization, for instance in the case of liver, renal or bone marrow failure.

ETHICS OF RANDOMISATION

Randomisation of patients (5,6) may initially appear shocking to the patients. Kassiner has even described it as an insult to the individual (7). This is true even if patients are in fact well-informed, both of the possible beneficial effects of a placebo and of the effects of no treatment (5,8,9), and of the fact that the relative advantages and risks of the two treatments to be compared are not yet known. In reality, however, many patients are not well-informed. It is even difficult to see how a placebo may be used with the full consent of family members, the family doctors and the patient.

It is, of course, important not to delay the development of more effective treatment. The purpose here is to try to propose ways to reduce patient discomfort and risk. The random choice between treatment and no treatment is useful in certain cases. It is not the purpose here to criticize all randomisations, or to establish an inventory of the technical defects of the randomisation methods. The present discussion deals only with the stage of minimal residual disease. In this stage, where patients are apparently healthy, ethical requirements are particularly important.

ETHICAL REQUIREMENTS FOR RANDOMISATION

When two treatments are to be compared, they must be selected to be the two most effective ones for the disease in question, there must be no known difference between them, but there must be at least a pilot study suggesting one. To launch a several year multi-center randomized trial without a promising pilot study is unacceptable. If an old treatment is known to be effective, frequently because it was compared with no treatment, the new treatment must be compared with the old one. This is generally accepted in theory, but in practice there are several trials (10–13) where the controls did not obtain the treatment which has previously been shown to be more effective than no treatment at all.

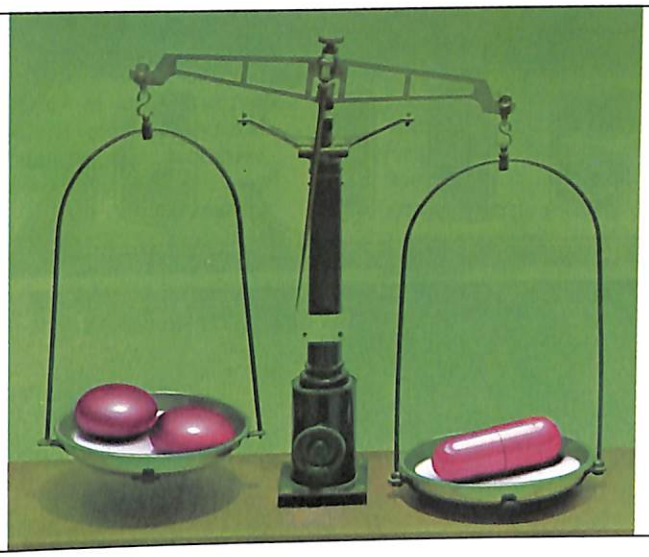
Repetitive randomized trials should be avoided, since it is always a disadvantage to be a randomized patient. There are, for instance, two randomized trials on patients with osteosarcoma, which only confirmed the 60% beneficial effect of chemotherapy that had been known of for 10 years (12,13), and one randomized trial of treatment with acyclovir, which only confirmed its well known effect on prevention of herpes virus infection (14).

The ethical requirements acquire increased importance now that studies seem to include an increasing number of subjects since the differences sought get smaller. This places a very large number of patients at both positive risk (toxicity) and negative risk (depriving them of another treatment).

CONCLUSION

In conclusion, the law requires that the scientific methodology must not reduce the patient's rights. The patient's right should be guaranteed, a priori, by ethics; rather than being debated, a posteriori, in court. Considering ethics before is better than having medicolegal problems after a clinical trial.

Erleichterung für den Leber-Patienten



= 420 mg

= 420 mg

Die bewährte Tagesdosis in der verbesserten Darreichungsform

Seit der Einführung von Legalon® 70 Dragées sind viele klinische Arbeiten publiziert worden, in denen die antihepatotoxische Wirkung von Legalon® bestätigt und untermauert wird. Darüber hinaus wurde die Tagesdosis von 6 Dragées Legalon® 70 (= 420 mg Silymarin) als optimal erkannt.

Um die Einnahme zu erleichtern, steht jetzt Legalon® 140 als Kapsel zur Verfügung, d. h. der Patient nimmt jetzt nur 3 x täglich 1 Kapsel.

Legalon® wird sehr gut vertragen und ist frei von Nebenwirkungen. Kontraindikationen sind nicht bekannt.

NEU **Legalon® 140**

MADAUS

Bessert die Leberfunktion bei akuten und chronischen Erkrankungen der Leber. **Zusammensetzung:** 1 Kaps. Legalon 140 enthält 140 mg Silymarin mit mind. 60 mg Silibinin in 200 mg Extr. Fruct. Cardui mariae. **Indikationen:** Als Adjuvans bei akuten und chronischen Hepatitiden wie Virushepatitis, aggressive und persistierende Hepatitiden, Leberzirrhose, toxisch-metabolische Leberschäden (z. B. Fettleber, medikamentöse Ursachen, Vergiftungen, Strahlenbelastung). **Dosierung:** Soweit nicht anders verordnet, in schweren Fällen 3 x täglich 1 Kapsel Legalon 140. **Handelsformen:** Legalon 140: O. P. mit 60 Kapseln

Dr. Madaus & Co. · D-5000 Köln 91 · Vertretung für Luxemburg: Integral S.A.

Not even comparative trials with a random selection will always produce reproducible results. The adjuvant chemotherapy effect on survival claimed by Rossi et al. (10) in pre-menopausal breast cancer was not found in an identical trial in the United Kingdom. Moreover, many women who received the treatment were later affected by severe bone marrow sequelae. The fact that these patients had severe complications of the probably inefficient adjuvant chemotherapy illustrates the ethical problem of randomisation.

Clinical trials must continue, but with the caution alluded to above. The International Society of Ethics in Cancer Research and the Committee of Ethics, where the discussions on which this paper is based took place, have proposed a three-pronged solution.

(a) Reduce the number of trials where promising pilot studies are missing or whose quantitative importance justifies neither the patient's discomfort nor the ethical problems following randomisation.

(b) Monitor the degree to which physicians respect the rights of each individual patient.

(c) Ensure that no trials are started that are impractical, repetitive or a threat to the patient's rights.

REFERENCES

1. LEE Y. L. and WESLEY R. A.: Statistical contributions to phase II trials in cancer: interpretation, analysis and design. Sem. Oncol. 8, 430, 1981.
2. GEHAN E. A.: Comparative clinical trials with historical controls: a statistician's view. Biomedicine 28, 13, 1978.
3. AUR R. J. A., SIMONE J. V., VERZOSA M. S., HUSTU H. O., BARKER L. F., PINKEL D. P., RIVERA G., DAHL G. V., WOOD A., STAGNER S. and MASON C.: Childhood acute lymphocytic leukemia. Study VIII. Cancer 42, 2123, 1978.
4. MATHÉ G., REIZENSTEIN P., HURTE-LOUP P., DELGADO M., GAGET H., GUILLERMO B., KEILLING R., MISSET J. L., MACHOVER D., QUENEAU P., SERMENT M., DION S. and GABAY M.: Le médecin, le statisticien, l'ordinateur dans la conduite des essais thérapeutiques et la casuistique du malade. Rapport 1984 sur le travail conduit grâce au contrat établi avec le C.N.R.S. dans le cadre du Programme: Science, Technologie et Société.
5. ARPAILLANGE P. and GASTON J. L.: Therapeutic trial and the applicable principle of law. Biomedicine 28, 57, 1978.
6. ARPAILLANGE P. and DION S.: Considérations sur l'éthique de la randomisation. Biomed. Pharmacother. 38, 426, 1984.
7. KASSINER J. P.: Adding insult to injury: usurping patient's prerogative. New Engl. J. Med. 308, 898, 1983.
8. WADA J. K., BOGDON D. L. and GUNNELL J. C.: Double-blind, randomized, crossover trial of nabilone vs. placebo in cancer chemotherapy. Cancer Treat. Rev. 9 (suppl. B), 39, 1982.
9. HERZHAFT G.: L'effet nocebo. Encéphale 58, 486, 1969.
10. ROSSI A., BONADONNA G., VALAGUSSA P. and VERONESI U.: Multimodal treatment in operable breast cancer: five-year results of the CMF programme. Br. Med. J. 282, 1427, 1981.
11. HOWELL A., GEORGES W. D. and CROWTHER D.: Controlled trial of adjuvant chemotherapy with cyclophosphamide, methotrexate and fluorouracile for breast cancer. Lancet ii, 307, 1984.
12. EILBER F. R. and ECKARDT J.: Adjuvant therapy for osteosarcoma: a randomized prospective trial. Proc. Am. Soc. clin. Oncol. 4, 144, 1985.
13. LINK M., GOORIN A., MISER A. et al.: The role of adjuvant chemotherapy in the treatment of osteosarcoma of the extremity: preliminary results of the multi-institutional osteosarcoma study. Proc. Am. Soc. clin. Oncol. 4, 237, 1985.
14. GLUCKMAN E., DEVERGIE A., MELO R. et al.: Prophylaxis of herpes infections after

bone-marrow transplantation by oral acyclovir. Lancet ii, 706, 1983.

15. PETO R.: Clinical trial methodology. Biomedicine 28, 24, 1978.

16. HESSE H.: The Glass Bead Game. London, Penguin, 1984.

Euglucon® 5

noch mehr Altersdiabetiker sind mit Euglucon 5 optimal einstellbar, denn nur Euglucon 5 setzt immer dann Insulin frei, wenn es gebraucht wird – nach jeder Mahlzeit.

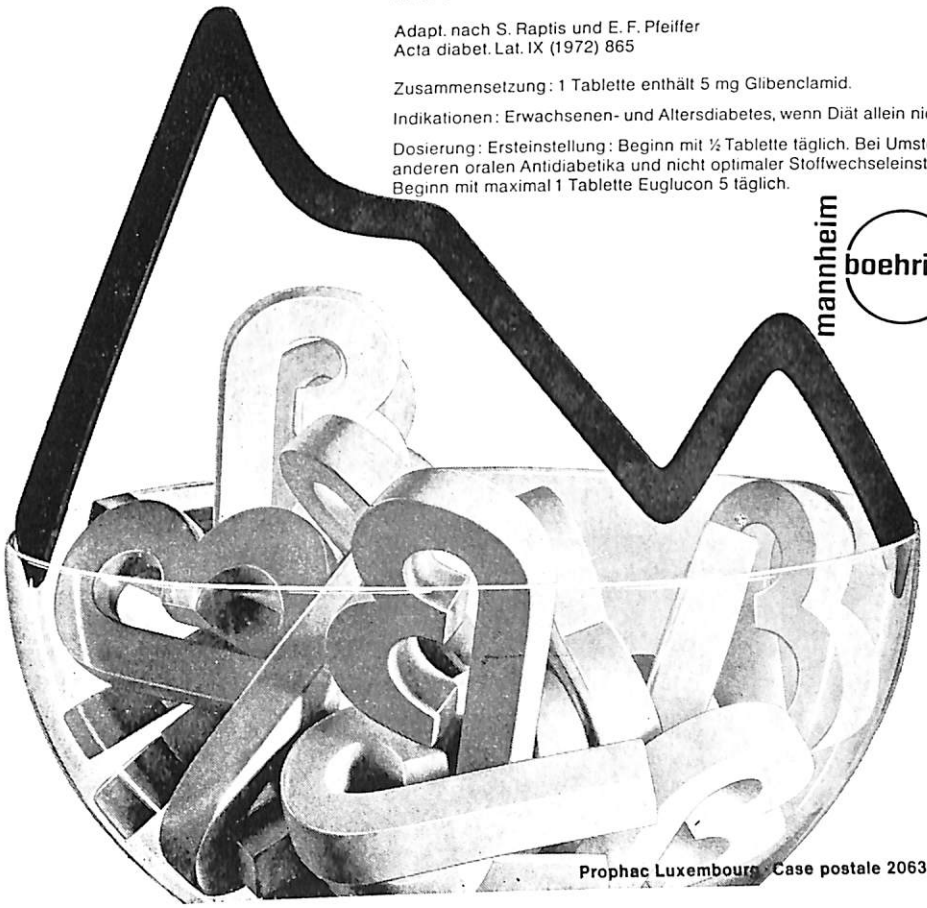
■ Insulinsekretion bei mit Euglucon 5 behandelten Altersdiabetikern in Relation zu den Mahlzeiten.

Adapt. nach S. Raptis und E. F. Pfeiffer
Acta diabet. Lat. IX (1972) 865

Zusammensetzung: 1 Tablette enthält 5 mg Glibenclamid.

Indikationen: Erwachsenen- und Altersdiabetes, wenn Diät allein nicht ausreicht.

Dosierung: Ersteinstellung: Beginn mit ½ Tablette täglich. Bei Umstellung von anderen oralen Antidiabetika und nicht optimaler Stoffwechseleinstellung: Beginn mit maximal 1 Tablette Euglucon 5 täglich.

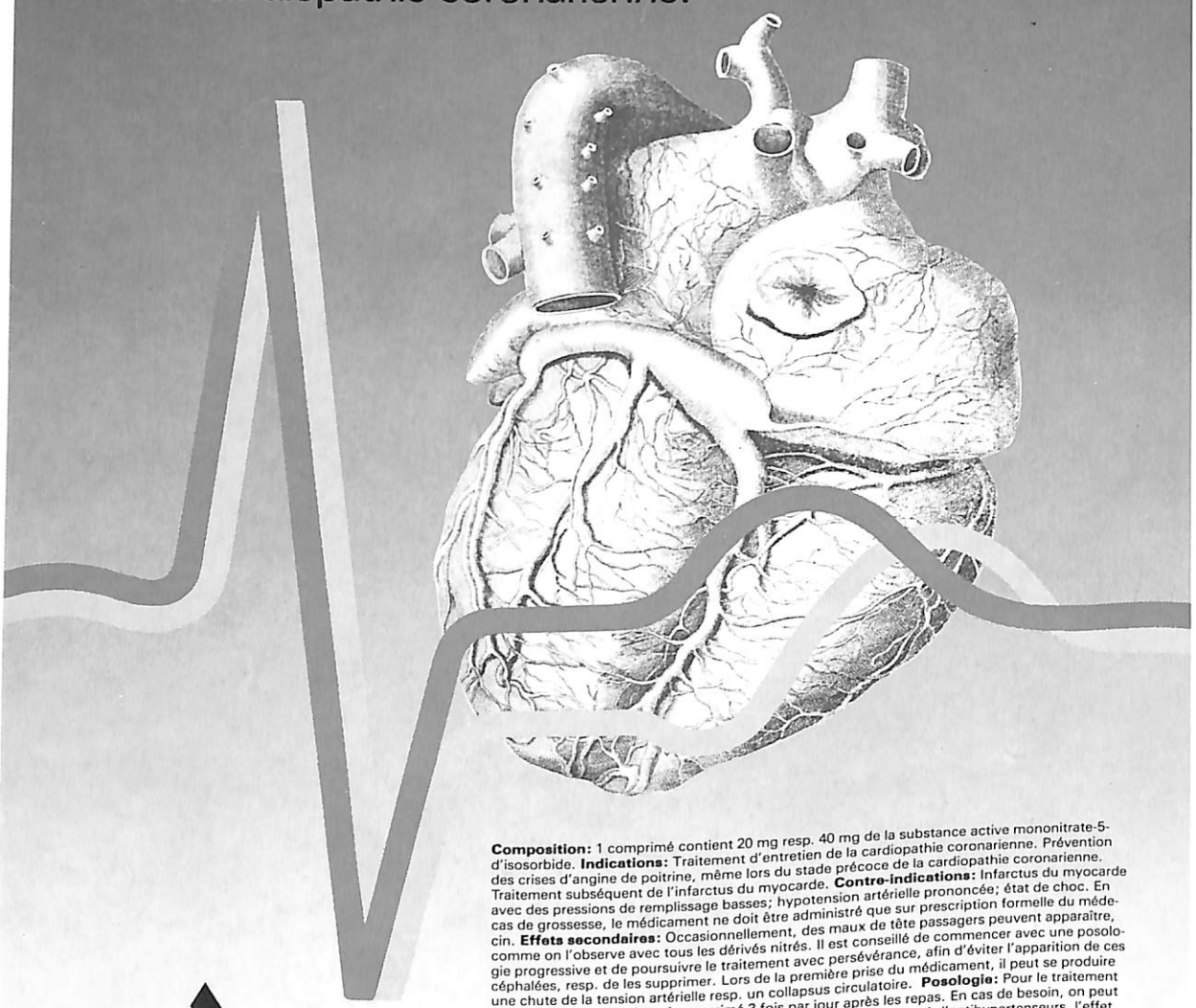


mannheim boehringer

Prophac Luxembourg · Case postale 2063 · Tél. 48 24 82

elantan®

un perfectionnement de
la thérapeutique
aux dérivés nitrés
pour le traitement d'entretien
de la cardiopathie coronarienne.



Composition: 1 comprimé contient 20 mg resp. 40 mg de la substance active mononitrate-5-d'isosorbide. **Indications:** Traitement d'entretien de la cardiopathie coronarienne. Prévention des crises d'angine de poitrine, même lors du stade précoce de la cardiopathie coronarienne. Traitement subséquent de l'infarctus du myocarde. **Contre-indications:** Infarctus du myocarde avec des pressions de remplissage basses; hypotension artérielle prononcée; état de choc. En cas de grossesse, le médicament ne doit être administré que sur prescription formelle du médecin. **Effets secondaires:** Occasionnellement, des maux de tête passagers peuvent apparaître, comme on l'observe avec tous les dérivés nitrés. Il est conseillé de commencer avec une posologie progressive et de poursuivre le traitement avec persévérance, afin d'éviter l'apparition de ces céphalées, resp. de les supprimer. Lors de la première prise du médicament, il peut se produire une chute de la tension artérielle resp. un collapsus circulatoire. **Posologie:** Pour le traitement d'entretien, on administre 1 comprimé 3 fois par jour après les repas. En cas de besoin, on peut aussi augmenter les doses. **Remarque:** En cas d'emploi simultané d'antihypertenseurs, l'effet de ceux-ci peut être renforcé. La consommation simultanée d'alcool peut provoquer une hypotension artérielle et ainsi une diminution de la faculté de réaction.

Pour la prescription: elantan 20: 50 et 100 comprimés, **elantan 40**: 50 et 100 comprimés

Sur prescription médicale

ADROSANOL

Adrosanol Pharma SA 4410 Liestal Industriestrasse 7 Téléphone 061.94 79 79

PROPHAC Luxembourg – case postale 2063 – Tél. 48 24 82