

Point of View

The Treatment of Human Cancer with Agents Prepared from Bovine Cartilage

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Summary: Oral and subcutaneous administration of specific preparations of bovine tracheal cartilage rings (Catrix), a nontoxic agent, has resulted in a high response rate in 31 cases of a variety of clinical malignancies (response rate 90%, 61% complete). The demonstrated responders include present therapeutic disasters such as glioblastoma multiforme and cancers of the pancreas and lung. Other types which were treated with success included cancers of the ovary, rectum, prostate, cervix, thyroid, and an inoperable squamous cancer of the nose. These responses were observed when full dose therapy was given over prolonged courses of treatment (years). This wide range of Catrix efficacy now invites investigation by others to confirm the effectiveness of the material and to isolate the molecular entities responsible for these unexpectedly favorable results. **Key Words:** Antimitotic—Cartilage—Catrix—Glycosaminoglycan—Immuno-stimulation—Mitogen.

The parenteral, oral, or topical use of Catrix has been demonstrated to accelerate wound healing (1-10), reverse the cortisone-induced inhibition of healing (11), possess powerful topical antiinflammatory capability, alleviate autoimmune diseases, relieve osteoarthritic pain to a greater extent than available nonsteroid antiinflammatory agents, reverse the dermal thickening and inelasticity of scleroderma, abort the skin manifestations of Herpes simplex (Type I) and zoster, permanently eliminate the pain of dry socket by topical application within minutes, and markedly alleviate (and often clear) the lesions of severe psoriasis through parenteral or oral administration (12).

Since the article in which the multiple clinical antiinflammatory uses of Catrix were reported (12), a total of 31 cancer patients have now been treated continuously with Catrix for a sufficient time to make a judgment as to possible efficacy. Both the parenteral and oral routes were utilized. This total includes, and this article reports, only those individuals who took Catrix consistently and followed instructions completely, since no estimate of Catrix efficacy can be made if these conditions were not met. About twice the number of patients reported here stopped treatment at various stages of Catrix therapy. The cause ranged from virtually no compliance to a patient's decision to discontinue treatment after several months of therapy. This decision was

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often the result of pressure from another physician to return to conventional chemotherapy, sometimes after it had already failed. No example of success attendant upon such a return is known. In no instance has clear treatment failure been "nonreported" as noncompliance, although it is recognized that noncompliance can be the result of patient dissatisfaction for reasonable or unreasonable cause.

The initial decision to test Catrinx in the clinical treatment of cancer was based upon its efficacy in a recognized proliferative model (psoriasis) (12); on its record of complete nontoxicity; and, in the first clinical case treated, upon the failure of all standard modalities of therapy in a patient whose cancer of the breast had ulcerated her entire chest wall, created another very painful ulcer over a large mound of supraclavicular metastases, and paralyzed her left arm.

Studies at Harvard and M.I.T. have shown the presence of an antitumor angiogenesis factor (anti-TAF) in bovine and shark cartilages (13,14). Catrinx administered to animal tumor models such as sarcoma-37, Ta3Ha, and Lewis lung tumors have shown favorable effects in work completed by Nowotny at the University of Pennsylvania (A. H. Nowotny, unpublished observations, 1983). Activation of mouse peritoneal macrophages in Catrinx-treated mice also has been demonstrated by Nowotny (A. H. Nowotny, unpublished observations, 1983) and confirmed by Johnson at the University of Minnesota (Duluth) (A. G. Johnson, unpublished observations, 1983). Durie et al. (15) have shown that Catrinx-S inhibits the survival of human cancer cells in stem cell cultures across a wide spectrum of cancer types, utilizing the techniques developed by Hamburger and Salmon (16), and Durie and Salmon (17). The principal assays on Catrinx utilizing this technique have been made by Durie et al., by employing the WIDR (colon), MCF (breast), and 8226 (myeloma) cell lines (15).

The principal wound acceleratory moiety contained within this remnant of the mesenchyme has been demonstrated to be polymeric *N*-acetyl glucosamine (18,19), probably most effective as the dimer. This polymer and its monomer have absolutely no demonstrable antimitotic effects in the stem cell assay, as demonstrated by Durie, who utilized colon, breast, and myeloma cell lines (15). Another of its components inhibits cellular division and inflammation, and appears to be of low molecular weight. This has been established by Gracy (R. W. Gracy, unpublished observations, 1984), who isolated potent fractions utilizing Amicon filter membranes, and then by subsequent testing in the human stem cell assay by Durie (B. G. M. Durie, unpublished observations, 1984), as well as by thymidine uptake assays utilizing the standard L-1210 tumor line by Ponzio (N. Ponzio, unpublished observations). Additional chemical characterization of these molecular cuts is required prior to publication of these interesting preliminary separations. The fact that oral therapy is effective, although to a lesser extent than is the parenteral route, also is indicative of a low molecular weight of the antimitotic molecular entities.

It is important to note that, while *N*-acetyl glucosamine lacks any inhibitory effect on cancer growth in these cancer cell culture test systems, glucosamine itself has significant inhibitory activity (15). This is consistent with reports of such activity by others (20,21).

MATERIAL AND METHODS

Preparation of Catrinx Powder

Catrinx powder is prepared from beef tracheas harvested at the slaughterhouse and immediately frozen at -70°C to prevent bacterial load. When convenient, the tracheas

are thawed and mechanically trimmed of all adhering tissues, cut into small chunks, and refrozen. When ready for final processing, the following steps are utilized. The tracheal chunks are treated with an aqueous solution of acetic acid and pepsin (NF grade) at 50–55°C for 5 h with gentle agitation. The pH is maintained at 3.2–3.6 by adjustment with 1 M HCl or NaOH (NF grade). The chunks are then washed thoroughly, covered with deionized hot water (50–60°C), and stirred for 30 min. A profuse cold water wash is performed to obtain maximal removal of the digested material, and the residual substance refrozen at –70°C. When convenient, the material is thawed and then ground in an auger-screw grinder using a plate with 1/8-inch holes. The ground trachea is suspended in NF acetone and stirred for 1 h, and then the supernatant liquid is drained. This step is repeated two additional times. The ground trachea is dried in a perforated bowl centrifuge at low speed until all visible liquid has been removed. The material is then spread thinly in stainless steel trays and dried overnight in a vacuum oven at 50–60°C. The dried, defatted Catrix is ground in a hammer mill using a screen with 1/16-inch holes; dry ice is added continuously to prevent charring and to aid in grinding the rubbery cartilage. A high-speed refrigerated hammer mill fitted with a 0.062-inch screen is then used to mill the Catrix. This step is repeated once. The powder is then ball-milled in a porcelain mill for 4 days, filling the mill so that the powder just covers the porcelain balls. After milling, it is passed through a 70- μ screen. The material held on the screen is reground, if the amount remaining makes this worthwhile. The average particle size is about 35 μ in the finished powder. Finally, the Catrix powder is dried again in a vacuum oven at 50–60°C overnight and then stored in double polyethylene-lined fiber drums.

The Catrix powder must meet specifications as follows: off-white or beige powder; maximum loss on drying is 5.00% (22); maximum residue on ignition is 3.00% (22); maximum heavy metals are 20 ppm (23); pH (10% suspension) 4.0–4.8 (24); maximum fat content is 0.50% dry basis (d.b.) (25); nitrogen, 11.0–14.0% d.b. (26); hexosamines, 7.80–10.50% (27); uronic acids, 5.90–8.00% (28); and hydroxyproline, 5.50–7.50% (29).

The powder is usually filled into gelatin no. 1 capsules to give 375 mg/capsule. Larger capsules may be made, but these sometimes cause problems in individuals with physical or psychological swallowing difficulties.

If these problems prevent adequate dosage, milk shakes or egg-nogs may be made each morning with the day's dosage (usually 24 capsules) added to the blender. The capsules dissolve readily, permitting the patient to drink the refrigerated milk shake at intervals during the day. The gelatin capsules add slightly to the viscosity of the drink.

Preparation of Catrix-S

Since preparation of Catrix-S involves adjustments of pH, solids, and volume, it is considered best to illustrate the method by the steps utilized in the preparation of a specific lot. The ingredients are Catrix powder, sodium chloride (USP), benzyl alcohol NF [quantum sufficit (q.s.) 0.9%], sodium hydroxide 50% solution (NF), and sterile water for injection (USP, q.s.). The following equipment is needed: Metromatic washer, Blue-M drying oven, autoclave, filimatic DAB 16, laminar flow hood DF323 Baker, and Gifford-Woods Homo-Mixer. The standard procedure for each piece of equipment is followed.

Procedure

Pour 195.0 L of water for injection into a stainless steel vessel and insert Homo-Mixer into the water and operate at medium speed. Slowly add the Catrix powder and mix until a uniform dispersion results, then add the sodium chloride and mix to ensure dissolution. Pour the mixture into individual liter bottles and autoclave the solution for 90 min at 121°C. Use biological indicators to record the cycle while autoclaving. Allow the solution to stand overnight after autoclaving. Filter the solution through a series of Millipore filters, ending with a sterile 0.22 μ filter. Final filtration should be done under the laminar flow hood, and with pressure less than 30 psi. Take a small sample and analyze it for total solids. The results in this preparation were: 7.18% total solids and 6.14% Catrix. The calculated values for water for injection, benzyl alcohol, and sodium chloride to achieve a final concentration of 0.05 g Catrix, 0.009 ml alcohol, and 0.009 g sodium chloride/ml for the final volume were: final volume needed, 299.6 L; sodium chloride, 158.4 g; water for injection q.s., 299.6; benzyl alcohol, 2690 ml. Add the benzyl alcohol, then add the sodium chloride and mix until dissolved. Adjust the pH to 7.2 ± 0.1 using 50% sodium hydroxide solution, and q.s. to appropriate volume, using sterile water for injection.

Filtration and Filling

Filter the final solution through a sterile 0.22 μ Millipore filter into a sterile receiving flask at a pressure <30 psi. Fill 51 ml into each sterile vial. Place the S-63 butyl gray stoppers in a vial, place a three-piece aluminum seal on the vial and crimp. Take vials to quarantine area for final inspection, labeling, and packaging.

Accounting

Submit samples of Catrix-S for testing of assay, sterility, pyrogenicity, and stability (see herein).

Specifications of Containers

The containers used were a 50-ml clear serum vial with a 20-mm opening, made of borosilicate glass, vitro "400." This meets the requirements of the United States Pharmacopeia for Type I glass. The stoppers were 20-mm pt-23 gray butyl stopper no. 1888, which were sealed with 20-mm aluminum 8-bridge white flip-off seals.

This particular preparation run produced 3,515 vials of Catrix-S containing 51 ml each for clinical use (some were withheld for chemical assay, sterility, pyrogenicity, and stability testing, as noted earlier).

The documentation accompanying the preparation of each lot of the injectable material includes the autoclave time chart, the certification of all reagents by their manufacturer, pyrogen and sterility assay by United States Pharmacopeia, 20th ed.-New Formulary, vol. XV methods, and specific chemical analysis as follows (Table 1). The results on the preparation referred to are given as test results. It is seen that they fall into the specification ranges.

In addition, a safety test (C.F.R., Title 21, 610.11) is utilized before the material is considered appropriate for clinical use. This involves the injection of 5 ml of the Catrix-S intraperitoneally in guinea pigs and 0.5 ml into mice with a 7-day period of observation. The animals exhibited no deleterious effects over this interval of time.

TABLE 1. Routine documentation of the content of this lot of Catrix-S

Parameter	Specification	Test results (this lot)
Hexosamine (27)	7.4-11.1%	8.75%
Hydroxyproline (29)	5.5-8.2%	6.57%
Uronic acid (28)	7.9-11.8%	9.29%
Total solids (30)	5.0-7.0%	6.09%
pH (24)	5.5-6.5	6.03
Particulate levels (31)	Free of visible particulate matter	Passes
Pyrogen (32)	Pyrogen-free	Pyrogen-free
Sterility (33)	Sterile	Sterile

Clinical Usage

The normal clinical oral dosage is 3 g every 8 h. Eight capsules, each containing 375 mg of the powdered Catrix, are taken every 8 h. Variations of this dosing are permitted if the patient prefers, in order that the taking of 24 capsules/day not disturb appetite, and therefore, nutrition. These variations range from 4.5 g every 12 h to one or two capsules whenever the patient feels able, the latter usually in patients with cancer-induced digestive problems. As noted, this problem is often solved by using "Catrix shakes." There is no evidence that dosing schedules are critical, providing at least 9 g/day are taken in at least two doses. Chronic diarrhea could be an exception, but this was not a clinical feature in this series except in the unusual circumstances of Case 31 (see treatment summaries).

While the maintenance dosage is given orally, the start of treatment is normally by injection. This is considered to be the loading phase. Prior to starting therapy by any route, we draw baseline chemistries and hematology, carcinoembryonic antigen (CEA), a special protein panel including immunoglobulin A (IgA), immunoglobulin G (IgG), and immunoglobulin M (IgM), and a lymphocyte profile determining T cell and B cell subsets by monoclonal antibodies (OKT and B-1). Baseline radiographs and scans appropriate to the cancer to be treated are obtained. In general, the chemistries and other tests are repeated at 3-month intervals initially if the condition is relatively stable. If clinical circumstances require it, appropriate increases in the frequency of office visits and testing, including possible hospitalization, are arranged.

After (and if) clinical success begins to be achieved, the frequency of visits decreases. Some of the original patients who were treated successfully are now seen only once a year, although reports are received from them and/or from their physicians every 2 months.

The treatment of cancer with Catrix began in 1972 and has progressed slowly because, with rare exceptions, only those for whom standard therapy had failed or was generally conceded to be of no value were accepted for therapy.

The patients reported here were part of a pilot study carried out with a demonstrably nontoxic substance in order to define variables which I will study later in rigorously controlled experiments. As noted, the general criteria for acceptance into treatment were that standard therapy of all kinds had failed, and that the patient agreed to the

treatment after a thorough discussion of its experimental nature, and that he or she had signed an explicit statement indicating that they had been informed of this.

The injection dosage form consists of the 5% Catrix solution (called Catrix-S) described previously. The 0.9% benzyl alcohol utilized as a preservative also acts as an anesthetic when the material is injected subcutaneously into depots. The usual dosage is 25–50 ml of the material into one area of the anterior thighs, abdomen, chest (below the breasts in women), flanks, and on the back, if the patient tolerates the latter site well. Lesser amounts may be given in smaller anatomical locations for specific purposes. Normally, two or four such injections are given at one visit to make the total dose per treatment 100 ml. This can be repeated as often as every other day, but is more usually given once a week. The initial loading period is considered adequate when a total of 2,000 ml has been injected. Normally, oral dosage then begins.

A review of the patient summaries will show that there has been considerable variation in this basic schemata. These variations were responses to changing clinical needs, bearing in mind that the injectable route is demonstrably more effective for all Catrix indications, and therefore should be utilized if the clinical response to oral dosage is unsatisfactory. The information gained from this experience has made it possible to design appropriate protocols for the controlled (IND) studies now beginning.

There is no perceived limit to the amount which can be given safely by any route, and there has never been toxicity in any patient on Catrix therapy.¹ On one occasion, 900 ml of Catrix-S was given subcutaneously to an anesthetized patient at one time without discernible problems of any kind. In addition, there have never been any abnormalities in the renal, hepatic, or hematologic blood values induced by Catrix therapy. This latter is a most important feature of this therapy because of the extraordinary contrast with the debility regularly induced by chemotherapy.

Amounts totaling 6,000 ml of Catrix-S have been given by injection over a number of weeks, the highest weekly rate being 800 ml; and oral administration has now reached a total of approximately 20 kg in several individuals, all without evidence of the development of any toxicity to the material. There is sometimes evidence of an initial local allergic reaction when Catrix-S is given by subcutaneous depot injection. This involves a local erythema, edema, and pruritus. Because of this possibility, 25 mg of diphenhydramine HCl (Benadryl) is given orally prior to the first four injections, and the first injection consists of a volume of 50 ml in one site rather than the customary two 50-ml injections in two sites administered thereafter. Despite several brisk reactions (an incidence of around 3%) of this type which occurred prior to the use of the antihistamine, there has never been an instance of a respiratory or other systemic reaction; and we regularly proceed with the injections at weekly or biweekly intervals. After 350 ml have been given, there has been no further reaction, and the diphenhydramine HCl is discontinued. This sequence of events appears to be a classical desensitization. The chemical source of the reaction to the initial injection is considered to be a very small amount of bovine protein not removed by processing.

¹Likewise, all FDA-mandated toxicity testing has been negative, including 2-year carcinogenesis and 16-month teratogenicity studies. The benign nature of the substance is illustrated by the difficulty or impossibility of determining an accurate LD₅₀, since the animals die at about the same volume of injection of the diluent.

TABLE 2. Stimulation indices^a

Mitogen	Mean of controls (13)	Range	Mean of treated patients (12)	Range	Standard error of difference between the means	Student's <i>t</i> test	<i>p</i>
PHA	132.1	37-428	390	40-1011	106	2.43	<0.025 >0.02
Con A	88.2	27-187	227.7	43-535	52	2.70	<0.02 >0.01
PWM	126.2	61-300	320.9	94-586	50	3.89	<0.001

PHA, phytohemagglutinin; Con A, concanavalin A; PWM, pokeweed mitogen.

^aStimulation index = number of counts per minute in stimulated (mitogen added) mixed lymphocyte culture/number of counts per minute of unstimulated (no mitogens) mixed lymphocyte culture of the same patient.

THE EFFECT OF CATRIX THERAPY IN HUMANS ON LYMPHOPROLIFERATIVE RESPONSES TO MITOGENS

In the course of the Catrix treatment, a total of nine cancer patients were tested to assess their lymphoproliferative response, utilizing the technique of Dean et al. (34) and Cannon et al. (35) with thymidine isotopic labeling. In two individuals the test was performed on multiple occasions. Controls were done on laboratory workers whenever a patient's response was evaluated. Each control determination was done on a different individual.

While the Catrix patients exhibited a significant increase in their stimulation indices (SI) as a result of the effects of phytohemagglutinin (PHA), Concanavalin A (Con A), and pokeweed mitogen (PWM) (Table 2), no differences could be demonstrated between the controls and Catrix-treated patients in the nonspecific esterase stain for macrophages or in the T cell rosette assay. This is believed to be due to the lessened sensitivity of these histological evaluations.

The increases in the lymphoproliferative response to mitogens secondary to Catrix therapy which have been demonstrated are statistically significant (Table 2). No definitive relationship to the duration of Catrix therapy has been established because of the lack of sufficient sequential sampling.

It is generally considered (35) that the average lymphoproliferative response to mitogens in cancer patients is lower than in the general population and that the response in those on chemotherapy is depressed even more. The data therefore indicate that the mitogenic increases demonstrated in Catrix-treated cancer patients are probably more significant than they appear on strictly statistical grounds.

The data were evaluated by a nonpairing technique, since the normals and cancer patients were obviously not pairable even if the media controls and mitogenically stimulated mixed lymphocyte cultures (MLC) were done on the same day.

These results give evidence that a significant modification of a biological (lymphoproliferative) response was induced by Catrix in human cancer patients. This, plus additional laboratory evidence obtained by others cited herein indicates that Catrix is a potent biological response modifier.

RESULTS

The treatment summaries and Table 3 give the details of the cases treated and the clinical results achieved. The cases have deliberately not been classified by the TNM

system, in the belief that a more complete understanding of each patient's status can be had by an explicit description.

Criteria of Response

Complete Response: Complete response is defined by disappearance of all clinical evidence of active tumor for a minimum of 12 weeks. This does not require total normalization of all involved radiographs; skeletal radiographs must clearly have improved with all the lesions showing evidence of reossification.

Partial Response: Fifty percent or greater decrease from baseline in the size of measured lesions (product of the tumor's largest measurement and its perpendicular diameter) or $\geq 50\%$ decrease in any pretreatment tumor markers was considered partial response. No simultaneous increase in the size of any lesions or markers or the appearance of new lesions or markers may occur and the response must be maintained for at least 12 weeks. If the liver size is being used as an indicator, there must be $>30\%$ decrease in the sum of three liver measurements below the costal margin, usually taken at the xyphoid, midclavicular line, and right costal margin.

Minimal Response: Minimal response was defined as tumor size decrease by $<50\%$ but $>25\%$ from baseline in the size of measurable tumor mass (the product of the tumor's longest dimension and its perpendicular diameter). Other parameters include 25–50% reduction in tumor markers, significant improvement in bone pain, and significant improvement in clinical neurological examination (brain cancer).

No Change: Objective tumor regression not qualifying for improved responses but lasting at least 12 weeks, or a steady state not qualifying for increasing disease of at least 16 weeks duration was defined as no change.

Progression: Unequivocal increase of at least 25% in the size of any measured lesions or tumor markers, or the appearance of any new lesion or marker was considered progression of disease.

Relapse: Relapse was defined as the appearance of new lesions, the reappearance of old lesions in patients who have achieved a complete response, or, for patients in partial response, increase of 50% or more in the sum of measurable tumor mass over that which was obtained at the time of maximum regression.

Duration of response was measured from the achievement of that response to the first sign of relapse. Duration of survival was determined from the point of start of therapy.

PATIENT TREATMENT SUMMARIES

Abbreviated patient summaries are presented in Table 3.

Case 1

F.K. was a 62-year-old woman when she began Catrx therapy. She had a massive ulceration of the entire left chest wall with invasion of the ribs, chest wall collapse, and a large supraclavicular mass with paresis of the left arm, secondary to neglected adenocarcinoma of the left breast. Her condition was followed by sequential biopsies, beginning in October 1972.

Her previous therapy consisted of radiation, estrogens, androgens, and chemotherapy, over 4 years. Initially, this therapy was effective but was soon followed by rapid and massive recurrence. The ulceration on the chest wall was 40×25 cm, with a left supraclavicular mass 8 cm in diameter. Chest films showed collapse of the left thorax with virtually no functional capacity.

Therapy Regimen

The Catrix dose regimen² was 100 ml/week subcutaneously, October 1972–July 1973; August 1973–August 1975, 100 ml subcutaneously at intervals of 1–6 weeks, increasing in frequency over 2 years; February 14–23, 1983, 150 ml/day subcutaneously; and February–November 1983, 9.0 g/day orally. There was no concomitant therapy. The patient died in November 1983.

Comments

Progressive reduction in massive chest wall lesions and supraclavicular masses occurred by June 1973. Ulceration resulted from continuing tumor necrosis. No residual cancer was found in tissue excised during a subclavian artery repair (June 1973), or in chest wall biopsies. She remained free of all disease in the left chest from 1973 until her death. Catrix was stopped in 1975 against advice. A new primary carcinoma in the right breast was diagnosed by biopsy in April 1976 and treated by modified radical mastectomy. Two axillary nodes were involved.

In April 1980, liver and bone scans were normal. In February 1983, a needle biopsy of one of many new pulmonary nodules throughout the right chest revealed poorly differentiated adenocarcinoma. Eight months later, a chest radiograph revealed only three distinct (and smaller) nodules remaining. However, she died in Florida in November 1983 of overwhelming genitourinary infection secondary to catheterization. No autopsy was done.

Outcome. Complete response (possible relapse); probable cure of initial cancer with recurrence of second breast primary cancer, not treated with Catrix.

Case 2

Z.H. was a 77-year-old woman when she appeared at Yale-New Haven Hospital in March 1973, with an inoperable, massive, neglected adenocarcinoma on the left breast. There was extension across the midline to the right breast and into the right supraclavicular space. She came for Catrix therapy with recurrent cancer spread across the entire chest wall following recurrence after radiation through three ports totaling 3,598 rad to the supraclavicular space on the right, 3,598 rad to the left chest wall and internal mammary nodes, and 5,694 rad to the chest wall and breast on the right. The voltage was 6 MeV. The first two courses took 29 days and the last, 47. Radiation therapy was finished May 11, 1973. She refused chemotherapy.

Therapy Regimen

The Catrix dose regimen was 100 ml/week subcutaneously, January 1976–January 1978; February–May 1977, 6 g/day orally; May–August 1977, 5.25 g/day orally; and August 1977–January 1978, 8 g/day orally. There was no concomitant therapy. The patient died in February 1978.

Comments

Initial chest films on March 18, 1975 had shown lymphangitic pulmonary metastases. Pulmonary metastases were absent from the radiograph by May 1977. A bone scan in January 1978 revealed possible metastatic lesions but no prior scan was available for comparison. A sputum sample taken in January 1978, at the start of the patient's pneumonia, was positive for metastatic cancer. Her death in early February, 1978 was due to pneumonia. Because of religious beliefs, the family would not permit respiratory therapy. The chest wall cancer ulcers had been healing steadily until she was admitted for pneumonia, with the large right supraclavicular mass decreasing from 6 cm to nonpalpability, and one 12-cm mass reducing to 1

²Total subcutaneous dosage shown represents multiple injections of Catrix-S solution into several sites, on a once-weekly basis unless otherwise noted. Oral doses in g/day represent administration of 375 mg Catrix capsules four times a day in equally divided doses. Doses in ml/day represent subcutaneous administration of Catrix-S solution. If dosing variations occurred, the dose shown represents an average for the period.

TABLE 3. Patient summaries^a

Patient, sex, age at start of Catrx treatment	Tumor type	Location, documentation, previous treatment	Pretreatment	
			Tumor measurements	Laboratory and radiologic data
1. F.K., woman, 62	Adenocarcinoma, breast	Entire chest wall including supraclavicular nodes. Nonresponsive to radiation, hormones, and chemotherapy.	40 × 25 cm at maximum diameters on chest wall. Supraclavicular mass about 8 cm in diameter.	Chest film showed collapse of left thorax due to invasion of ribs and pathological fractures.
2. Z.H., woman, 77	Adenocarcinoma, breast	Involvement of entire chest wall. Brief response to radiation through three separate ports (left chest, right chest, supraclavicular space); refused chemotherapy.	Right supraclavicular mass of 6 cm and mass over left internal mammary chain of 12 cm in diameter. Many other cancer ulcers.	Chest films showed lymphangitic metastases when treatment was begun.
3. L.T., woman, 60	Adenocarcinoma, breast	Bone lesions in thoracic spine and T-11 collapse by radiographs and bone scans. Scan positive in hips, pelvis and skull. 4000 and 3200 rad of radiation helpful for thoracic and right hip pain. Estrogens of no benefit.	Alkaline phosphatase and CEA about 200 mu/ml and about 160 ng/ml, respectively, prior to Catrx treatment (normals up to 105 and 5 respectively).	No biopsies obtained before Catrx radiograph because of typical radiograph findings and chemistries.
4. M.B., woman, 57	Adenocarcinoma, breast	Left radical mastectomy in March 1968, radiation and chemotherapy (details not obtainable) 1968-70; Thiotepa, androgens, Cytosan, March-June 1974; 5-FU and methotrexate, June 1974-September 1975; Catrx treatment begun August 1976.	Largest ulcer on chest wall was 12 cm in diameter. Mass in right axilla was 6 cm.	No demonstrable distant metastases by film. Alkaline phosphatase and CEA normal.
5. O.H., woman, 63	Papillary cystadenocarcinoma of the ovary	At original exploration, only biopsies done due to peritoneal carcinomatosis. Melphalan 6 mg/day, 5 days/month from June 1976-September 1977 without improvement. Began Catrx in April 1978.	Pelvic mass 10 cm in diameter with partial obstruction to rectum. Multiple abdominal masses averaging about 6 cm in diameter with bulging ascites.	Flat film showed high diaphragms and ascites. Clear lung fields in chest film. Liver chemistries normal, anemic with Hb of 10.00 gm%.
6. M.H., woman, 58	Carcinoma <i>in situ</i> of cervix	She had declined all proffered treatment, including radiation and hysterectomy.	On speculum exam, there was an inflamed area about the os measuring 2 cm in diameter.	Pap smears had been Class III and IV for more than a year prior to biopsy showing cancer in November 1977.
7. P.G., woman, 57	Leiomyosarcoma of left broad ligament in 1973.	Had supracervical hysterectomy in 1973 followed by 5000 rad radiation through two pelvic ports. Metastases to right lower lobe of lung in July 1975, to cervical stump in January 1977, and repeatedly to left posterior thigh until June 1980. Right lower lobectomy in July 1975, excision of cervical stump in January 1977, and repeated aspirations of fluid and excisions of subcutaneous tissue and muscle in posterior thigh until June 1980.	No tumor available for measurement at start of therapy. No demonstrable metastases at that time. Subsequent events proved its presence (see post-treatment data).	The various metastases noted were histologically typical of the original leiomyosarcoma.
8. L.A., man, 81	Adenocarcinoma of prostate.	Diagnosis at TUR in March 1976. Treated with 1 mg/day DES from start. Refused castration.	Original size of medial lesion not noted on Op Note. Subsequent recurrence documented as 2 cm right lobe nodule in June 1977.	When recurrent nodule appeared, acid phosphatase 22 ng/ml (normal high 11 ng/ml), and bone scan demonstrated metastases in right 10-12th ribs and pelvis.
9. R.G., man, 60	Adenocarcinoma of prostate.	TUR, September 1976. Widespread metastases shown in bone scan. DES at 1 mg b.i.d. effective until October 1977. Stopped with intense pain and widespread recurrence in bone.	Scans showed cancer in spine, ribs, clavicles, pelvis and hips. Prostate about 2× normal and rock-hard when first seen.	Scans and histology as indicated. Acid phosphatase 47.3 ng/ml at start of Catrx.
10. W.S., man, 62	Adenocarcinoma of prostate.	Cytoscopy and perineal needle biopsy, October 1976. Took DES 1 mg b.i.d. for two months.	Original nodule in right lobe was 6 cm, went to 2.5 cm on DES.	Acid phosphatase became normal on DES, returned to abnormal (20 ng/ml) when stopped. Bone scan negative.
11. W.T., man, 61	Adenocarcinoma of prostate.	TUR in August 1979. Declined DES, radiation, and surgery. Catrx was begun September 1982.	Nodule 3 cm in diameter in right lobe, with protrusion through capsule.	Acid phosphatase 56 ng/ml at start of therapy. Bone scans negative in September 1980 and August 1981.
12. G.D., man, 54	Adenocarcinoma of the rectum.	Diagnosed by multiple biopsies and colonoscopy. Patient declined surgery, chemotherapy, and radiation.	Rectal mass 14 cm in diameter (filled rectum and impinged on bladder).	Biopsy material also showed villous components.
13. W.D., man, 79	Adenocarcinoma of the rectum.	Diagnosis by multiple biopsies. Patient declined surgery, radiation, and chemotherapy.	Mass was 12 cm in diameter with deep invasion of ischiorectal space on right.	Biopsies showed aggressive histology, but no nodes or liver metastases demonstrated.
14. M.K., man, 50	Adenocarcinoma of splenic flexure.	At original colectomy, no nodes or distant metastases seen despite its large size with mesocolon invasion. Recurrence found on barium enema in July 1975 and confirmed by colonoscopy.	The recurrence was also a large mass (12 × 6 × 6 cm), half the size of the original tumor.	No evidence of liver metastases, but left diaphragm appeared involved by chest films.
15. W.G., man, 65	Adenocarcinoma of hepatic flexure.	Right colectomy with excision of anterior wall of duodenum done February 1982. No nodes involved. Reobstruction in October 1982, resection of anastomotic recurrence and of involved jejunal loop. No nodal or liver involvement demonstrable.	At inception of Catrx treatment, mass of about 5 cm in RUQ.	Pathology specimen at second operation showed extension of cancer to resection line. CEA rose to 15 ng/ml before Catrx started.
16. A.F., man, 61	Adenocarcinoma of gastric cardia.	Esophago-gastrectomy in May 1975. Anorectic by October 1975, when endoscopy showed recurrence at anastomosis.	Extrinsic mass effect at endoscopy was difficult to quantitate.	Biopsies of recurrence consistent with the primary lesion.

TABLE 3. (contd.)

Posttreatment		
Tumor measurements	Laboratory and radiologic data; present status	Classification of response
Entire tumor mass on chest wall and in left supraclavicular area completely disappeared.	Fractures of left ribs healed without reexpansion of hemithorax. Stopped Catrix against advice in 1975. Died of uncontrolled urinary sepsis unrelated to cancer in November, 1983.	Complete response (?relapse); probable cure of initial cancer with recurrence of second breast primary cancer, excised in 1976 without Catrix treatment.
Many of the innumerable chest wall lesions disappeared. The 12 cm lesion shrank to 1 cm. In general, decrease in ulcers and masses was about 90%.	The lymphangitic lung metastases disappeared in two months. Death in February 1978 from pneumonia; no autopsy.	Partial response; death due to incompletely treated pneumonia.
Pathological fracture of right hip led to excision of head and neck of femur one year after Catrix begun. No cancer in specimen. Needle biopsy of lower spine five years after Catrix treatment begun showed recurrence; Tamoxifen 10 mg/day started then.	CEA and alkaline phosphatase decreased to 20 and 60 (both normal) respectively. Patient works steadily as a concert violinist.	Partial response (with relapse); fully active 7 years after Catrix begun.
Largest ulcer on chest wall went to 5 × 3.5 cm, and right axillary mass went to 1.25 × 1.25 cm in August 1977.	No change in biopsy histology during Catrix treatment. Death due to cardiac arrest after admission for congestive failure.	Partial response; cardiac death.
The pelvic mass disappeared in three weeks, as did ascites. All palpable abdominal masses were gone in six weeks. At operation for acute cholecystitis in October 1978 (same surgeon), no tumor found in peritoneum, all biopsies negative.	Following husband's death (February 1980), stopped food and Catrix and developed abdominal, pleural, and supraclavicular recurrences. Died February 1982.	Complete response; relapse and death following cessation of treatment.
The 2 cm inflamed area gradually became less abnormal in appearance, and appeared normal by August 1978.	Pap smears went from Class IV to Class I by May 1978, and biopsies showed mild dysplasia until August 1978. Biopsies thenceforth normal. Last Pap smear Class I in January 1985. Excellent health as of May 1985.	Complete response; probable cure (7 years).
A 2.5 cm metastatic nodule appeared in the right buttock in October 1983. It was excised.	The nodule showed a small collection of leiomyosarcoma cells surrounded by histiocytes. A pathologist unaware of the treatment cited evidence of immune reaction. Patient feels very well.	Complete response; with relapse and ongoing second complete response (as defined).
Right lobe nodule disappeared by March 1978, but reappeared in May 1980 after prolonged period on lower Catrix dose. Return to higher dose caused final disappearance in June 1980.	Acid phosphatase levels fell with the disappearance of the right lobe nodule. Perineal needle biopsy showed no tumor in October 1981. Patient was well, vigorous, off DES as of March 18, 1985.	Complete response; recurrence after long period of Catrix therapy; questionable synergy with DES.
Prostate shrank to normal size by December 1977. Bone scan showed prompt disappearance of all lesions (in 12 days). After three asymptomatic years, bone and subdural recurrences unresponsive to chemotherapy and radiation appeared.	Acid phosphatase at start of Catrix (October 12, 1977) was 47.3, on October 25, 1977 it was 11.7, and 6.9 on November 16, 1977. It remained normal until March 1981, and then rose gradually over 1981 to ~50 ng/ml. Died with paralysis and progression in October 1983.	Complete response; relapse after 3 years of Catrix; rapid progression to death despite radiation and chemotherapy.
Prostate nodule gradually shrank to entirely normal by January 1979 and did not reappear over following five years.	Despite complete absence of chemical or physical evidence of disease, a few prostate cancer cells were found in June 1981 by perineal needle biopsy.	Complete response; possible cure; sudden cardiac death.
Prostate gradually increased in size on Catrix alone to 3× normal and rock-hard by November 1981. Rapidly decreased to normal when DES added in November 1981. Escaped DES control in December 1984, went to ketoconazole and Catrix with return to normal prostate size.	Acid phosphatase fell on ketoconazole from >60 ng/ml to normal at 8 ng/ml. Radiation therapy started elsewhere despite presumptive response to ketoconazole because of possible neck and pelvic metastases by bone scans. He now (May 1, 1985) feels well and is fully active 5½ years after diagnosis.	No response to Catrix alone (increasing disease). Responses to concomitant DES first, then to ketoconazole.
Rectal lesion decreased steadily in size under sequential sigmoidoscopic observation to two small stalked polyps, both of which were removed in December 1975. Colonoscopy showed transverse colon lesions gone.	All clinical chemistries continue normal. He has gained 20 lbs and feels well.	Complete response; probably cure (11 years).
Almost 50% reduction in size of cancer by November 1977. By April 1978, only an ulcer without mucosal coverage remained. Destruction of sphincter made end sigmoid colostomy (March 1979) necessary.	Ten biopsies between April 1978 and April 1979 revealed no malignancy. Became senile. Sudden cardiac death in nursing home August 1979.	Complete response; possible cure; cardiac death.
Consecutive estimates of tumor size by barium enemas showed shrinkage through April 1976.	The liver chemistries remained normal. Chest films showed pneumonitis and fluid in left lower lung. Patient died of a posterior wall myocardial infarction in July 1976. Autopsy showed extensive necrosis throughout the recurrent tumor mass. Viable tumor cells were present.	Improved response; possibly influenced by concomitant 5-FU; cardiac death.
From the start of Catrix treatment, the mass in RUQ diminished and disappeared.	CEA has remained at about 6 ng/ml for 15 months. Excellent appetite. Feels well.	Complete response; possible cure at 2.5 years.
All evidence of tumor disappeared by repeat endoscopy in 4 months. After a recurrence of symptoms, reexploration revealed 2 cm fibrotic reaction to cancer about anastomosis, small metastases (a 1 cm node in left hepatic lobe, and at least one 1 cm metastasis in colic nodes).	Liver chemistries remained normal. Died of a pulmonary embolism confirmed at autopsy, which revealed no change from the status at surgery 7 months before.	Complete response; with relapse; probable synergy with 5-FU with relapse after its cessation; death due to embolism.

TABLE 3. (contd.)

Patient, sex, age at start of Catrix treatment	Tumor type	Location, documentation, previous treatment	Pretreatment	
			Tumor measurements	Laboratory and radiologic data
17. E.H., woman, 73	Adenocarcinoma of stomach.	Massive size documented by gastrointestinal series and gastroscopy. Patient had refused all treatment for 1 1/2 years.	Initial size was 24 × 12 cm by palpation when Catrix begun May 1977.	First diagnosis by gastroscopic biopsy which confirmed size estimated by palpation.
18. E.M., man, 63	Adenocarcinoma of the head of the pancreas.	Cholecysto-jejunostomy with biopsies February 1977. Liver metastases.	By the time Catrix begun in May, 1977, a 20 cm mass present in RUQ.	Alkaline phosphatase was 300 mu/ml (with high normal of 150). CEA was about 50 ng/ml.
19. M.G., woman, 60	Adenocarcinoma of pancreas.	Metastases to the liver occupying entire right abdomen. Documentation by palpation, CT scans and needle biopsy. No previous treatment. Had had Catrix treatment for arthritis of neck (12) with complete relief; discontinued 7 months previously.	As noted, liver filled entire right side of abdomen and CT scan showed 5 cm mass in body of pancreas.	Alkaline phosphatase, transaminases, bilirubin, and CEA all about 2× normal at start of Catrix treatment.
20. P.A., woman, 69	Adenocarcinoma of the head of the pancreas.	Pancreas and involved regional nodes removed by Whipple procedure with findings noted. No other treatment.	The primary mass was about 8 cm in diameter.	Liver chemistries were normal except for mild elevation of alkaline phosphatase at start of Catrix treatment.
21. J.P., man, 45	Squamous cell carcinoma, lung	Bronchoscopy and right upper lobectomy. Operation done despite gross invasion of apical pleura. 10,000 rad given through three ports. Methotrexate, Adriamycin, and Cytoxan given February 1978 through May 1979 with minimal initial regression followed by regrowth and increasing pain and arm dysfunction. Platinol without effect May 1979 to September 1979.	By September 1977, there was radiographic and clinical evidence of invasion of the brachial plexus and transverse processes at C-6 and C-7. Right supraclavicular mass about 8 cm in diameter.	Neurologic consultation confirmed median and ulnar nerve paresis.
22. J.P., man, 63	Squamous cell carcinoma, lung	Entire left lower lobe diagnosed first by bronchoscopy, and later at left thoracotomy, August 1976. Large numbers of mediastinal nodes involved at operation. Radiation totaling 6000 rad through two ports given October-December 1978.	As noted, the tumor replaced the left lower lobe, in addition to the mediastinal involvement.	Following RT, the mass disappeared by chest film as did the mediastinal enlargement. Catrix begun immediately after RT completed.
23. M.M., man, 73	Squamous cell carcinoma, lung	Bronchoscopic biopsy in April 1975. The tumor was resectable but severe chronic pulmonary insufficiency made both thoracotomy and radiation impossible.	The biopsied abnormality was 1 cm in diameter.	Sputum cytology was Class V. All chemistries normal initially.
24. A.H., man, 71	Squamous cell carcinoma, lung	Bronchoscopic biopsy June 1975. Declined surgery; 5000 rad given through two ports with disappearance of lesion by bronchoscopy.	A 2 cm area of abnormality was biopsied.	Class V sputum cytology with fragments of cancer. Small lesion visible on films changed to fibrotic streaks after RT.
25. C.R., woman, 82	Two large basal cell carcinomas.	The lesions were between the rib margin and the iliac crest. Innumerable inadequate excisions had been attempted elsewhere. Radiation to 6000 rad had no effect.	The right lesion was 15 × 12 cm and the left 12 × 10 cm. She refused radical excision on three occasions.	Numerous biopsies confirmed basal cell carcinoma.
26. F.V., man, 59	Basal cell carcinoma.	Tumor was already beyond surgery, invading ribs and destroying the anterior thoracic and abdominal walls through pleura and to peritoneum. Radiation up to 9000 rad had no effect.	Diameter was 30 cm (Fig. 3). As noted, there was collapse of anterior thoracic wall.	Films showed about 50% loss of volume in right chest.
27. D.G., man, 79	Squamous cell carcinoma, nose.	The entire nose was involved (Fig. 5). Since all doctors consulted believed it to be secondary to excessive fluoroscopic work in his office, radiation was not possible. Patient refused excision of his nose.	Despite involvement of entire nose, there have been no nodal metastases. Multiple malignant ulcers and nodules were present.	Photographed (Fig. 5).
28. F.P., man, 21	Hodgkin's disease, upper mediastinum.	The tumor occupied 50% of the transverse diameter of the chest at the level of third sternal-chondral junction. He refused radiation and chemotherapy for almost 2 years. Supraclavicular nodes present at both sites.	Size as noted.	The tumor was of mixed cellularity. CT scans showed no evidence of disease below diaphragm.
29. D.W., woman, 79	Right renal cell carcinoma	Nephrectomy in January 1976. Metastases to left upper lobe followed by lobectomy in August 1976.	Multiple bilateral pulmonary metastases up to 8 cm in diameter appeared by May 1978.	CT scan in May 1978 showed a large metastasis high in right lobe of liver measuring 12 cm in diameter.
30. E.S., woman, 59	Glioblastoma multiforme (Grade IV)	Direct invasion of skull was demonstrated at craniotomy which followed a work-up induced by a convulsion. She declined chemotherapy and took only 600 rad of radiation before withdrawing permission due to hair loss.	The tumor occupied most of the right frontal lobe at operation.	Baseline CT scan confirmed operative impression of size.
31. M.C., woman, 59	Medullary carcinoma of thyroid.	Metastatic to right supraclavicular space, to mediastinum inferiorly and to the right bronchus. Had had radical total thyroidectomy with right radical neck and mediastinal dissection. Declined radiation and chemotherapy. Bone scan showed metastases in right clavicular head and right fourth rib.	Mediastinal mass was 7 × 2.3 cm at start of Catrix (on chest film) in September 1982.	Surgical pathology showed tumor cut across at the inferior edge of the mediastinal dissection. Calcitonin was 9710 pg/ml, falling to 1700 postoperatively. Gradual increase to 16,000 at the start of Catrix treatment.

CT, computed tomography; DES, diethylstilbestrol; CEA, carcinoembryonic antigen; RT, radiation; TUR, transurethral resection; RUQ, right upper quadrant.

TABLE 3. (contd.)

Posttreatment		
Tumor measurements	Laboratory and radiologic data; present status	Classification of response
Tumor shrank to a 3 cm diameter nodule in RUQ and pyloric obstruction occurred. This was removed at operation in August 1977. No other cancer found in peritoneal cavity. Pelvic (Krukenberg) tumors removed in September 1978.	First pathology specimen showed only rare cancer cells in fibrotic mass. Gained 18 lbs over following year. Stopped Catrux July 1978. Ovaries removed in September 1978 showed extensive necrosis in one, necrosis and viable cancer in the other. Liver scan had shown hepatic metastases in December 1978. Died February 1979.	Complete response; relapse after Catrux discontinued.
Palpable mass disappeared by September 1977. Shrinkage confirmed by ultrasonography and CT scanning.	A liver isotopic scan had been negative for the first time a month before the pneumonia. He had survived 17 months with widespread cancer of the pancreas. Had gained 15 lbs prior to onset of pneumonia (untreated elsewhere).	Partial response; demonstrated shrinkage of primary tumor and liver metastases; death due to untreated pneumonia.
The liver shrank rapidly until it was no longer palpable.	After a period of marked improvement, liver chemistries became characteristic of acute hepatic failure (about 3× normal). Autopsy showed no gross tumor remaining, although a few microscopic strands were seen in liver and pulmonary lymphatics.	Complete response; death due to tumor necrosis in liver, with hepatic functional failure.
No recurrence of tumor mass.	The alkaline phosphatase rose to ~1000 μ/ml (normal to 150) and the transaminases and bilirubin were about 3½ normal until improvement began. She now feels very well and all chemistries are normal.	Complete response; probable cure (8 years).
The right supraclavicular mass regressed completely. Chest films showed clearing of apical shadow by about 50%. Pain decreased considerably. After 4 months of improvement, ataxia and general leg aches began in December 1980. Posterior laminectomy showed a fibrous collar around spinal cord, immediate relief.	Right supraclavicular region biopsies were all negative. The fibrous ring encompassing the spinal cord contained a sparse population of cancer cells. Died on evening of first postoperative day after reexploration of laminectomy wound for bleeding. Probably cardiac death.	Partial response; demonstrated absence of cancer in original sites; death following operative excision subdural metastases.
By April 1979, there was a reappearance of the mass in the original area. This slowly increased in size until September 1979 after which it markedly decreased. It stabilized at about 12 × 7 cm on films. In April 1980, a 2 cm tender node appeared in right supraclavicular space with a 3.5 cm mass in superior mediastinum interfering with swallowing. 3000 rad of radiation to area was given April–June 1980.	Left chest mass remained constant radiographically while, as noted, the right superior mediastinal mass disappeared by barium swallow after radiation. He was not actively treated for viral pneumonitis and died early in April 1981.	Partial response; relapse in mediastinum after year and a half; responded to radiation; death due to untreated pneumonia 2½ years after Catrux began.
Bronchoscopy in August 1979 showed no evidence of tumor, nor did repeat chest films. Gained weight steadily: 10 lbs by March 1977 and 20 lbs by June 1978. He began to miss appointments (in July 1978) and had frequent drinking bouts. In August 1979 he was put in a nursing home by family. Catrux not taken there (due to regulations).	His sputum cytology became negative (Class I or II) following the start of treatment and remained so until he was lost to follow-up. A CT scan in August 1979 showed metastatic lesions in the liver, and his alkaline phosphatase doubled. Not biopsied due to family opposition. He died of a cardiac event in the nursing home in November 1979.	Complete response; relapse and death 4½ years after diagnosis made.
Bronchoscopy not repeated at patient's insistence. Constant psychiatric problems.	Sputum cytology went to Class I promptly, and remained so until his death in December 1976 due to pentobarbital overdose.	Complete response; possible cure; possible synergy with radiation; death due to pentobarbital overdose.
The left-sided lesion healed slowly but steadily and remained healed after July 1978. The right-sided lesion underwent considerable necrosis and ulceration. Eventually the right ulcer reduced by about 50% (Figs. 1 and 2).	Reduced but definite amounts of basal-cell cancer remained in the right-sided biopsies. Death at another institution in October 1983 was due to viral pneumonia as a culmination of inability to care for herself at the age of 87.	Partial response; death due to viral pneumonia at age 87.
Lesion area had reduced by about 30% by January 1979. Progressive filling of ulcer with granulation until July 1980 when progress halted due to fibrosis (Fig. 4).	Biopsies showed regressive cancer until June 1982, when no cancer was seen microscopically. His family, wearying of the burden, arranged admission to a cancer center where they planned total excision over the patient's (and my) objections. He was afraid of this prospect and bled to death of a gastric ulcer the night before the scheduled operation (March 1983).	Partial response; continual slow improvement; death due to gastric hemorrhage.
Progressive healing of malignant ulcers and flattening of nodules (Fig. 6).	Biopsies of both sides of the nose in April 1985 showed actinic dermatitis on right and basal cell carcinoma cells on left.	Complete response; probable cure.
Tumor remained of constant size for almost 2 years. The supraclavicular nodes were removed on two occasions and showed considerable fibrosis. After he accepted radiation and Mustargen Oncovin prednisone procarbazine (MOPP), mass gradually disappeared.	He feels well after 2 years of stabilization on Catrux alone.	No change; chemotherapy required to reduce mass after 2 years stabilization.
Bilateral pulmonary metastases gradually disappeared although CT scan still showed the liver lesion.	Chest films showed a dramatic disappearance of the metastases, however, the CT scan showed the liver metastasis to increase in size. She gained 10 lbs and strength until a stroke in September 1979 required admission to a nursing home. She died shortly after onset of severe abdominal pain in February 1980. Postmortem showed this to be due to accumulation of necrotic debris rather than to tumor growth. No residual cancer was found anywhere, grossly or microscopically.	Complete response; probable cure; death due to peritonitis.
The tumor decreased on progressive CT examinations as did her initial headaches and eye symptoms. By April 1979, no tumor was demonstrable.	CT scans and skull films showed return to a normal pattern by April 1979. She feels entirely well.	Complete response; probable cure (7 years).
Mediastinal mass decreased to 3.5 × 1.0 cm by May 1984 (an about 80% cross-sectional diminution) and has since remained constant. Clavicular head has remained constant in size, but is no longer painful.	Bone scan has not been repeated, chest films are unchanged. Calcitonin has increased from 6000 to 9600 pg/ml, yet CEA has decreased from 64 ng/ml to 32 at the same time. She gained 10 lbs and had much more energy.	Partial response; relapse probably related to dosage noncompliance.

^aConsult treatment summaries in text for Catrux dose regimens, concomitant therapies, and detailed clinical course descriptions.

cm and becoming freely movable. In general, the multiple nodules and ulcers had decreased by approximately 90%.

Outcome. Partial response; death due to incompletely-treated pneumonia.

Case 3

L.T., a 60-year-old woman, had a modified radical mastectomy in 1975 for a low-grade adenocarcinoma of the left breast. The nodes were negative. In 1978 she experienced severe back pain, and films showed T-11 vertebral body collapse and multiple osseous metastases in the axial skeleton, pelvis, and upper femora but no lymphadenopathy was present. No biopsy was done at this time because of the high alkaline phosphatase and CEA levels in the blood, together with the typical radiograph findings. Estrogens were given for 4 months without effect, and she refused chemotherapy. She accepted 4,000 rad of radiation over the lower thoracic spine, and 3,200 rad over the right hip. Following this, Catrix therapy was begun.

Therapy Regimen

The Catrix dose regimen was 9 g/day orally, June 1978–August 1983; July–November 1980, 250 ml/week, subcutaneously, was added to the oral dose. From August to October 1983, the patient received 13.5 g/day orally; and November 1982–present, 9 g/day orally. Concomitantly, she received prednisone at 5–40 mg/day, June 1980–October 1984; and October 1984–present, tamoxifen citrate at 10 mg/day.

Comments

The patient's alkaline phosphatase level became normal by September 1978. In February 1979, radiographs showed conversion of metastases from osteolytic to osteoblastic. A hip replacement in March 1979 showed the resected head and neck of femur to be free of cancer. Many histocytes were observed in the microscopic sections. Her alkaline phosphatase was elevated during the period from July 1979–November 1980, peaking in July 1980 at 300 U/L (normal high = 160), and then returning to normal. Low doses of prednisone were begun at this time to relieve the pain. A slow but steady elevation of CEA from June 1978 to late 1980 was followed by a decrease in CEA to a plateau that remained significantly elevated at ~65 ng/ml until January 1984, when it decreased to 9 ng/ml. A 3-cm lymph node appeared at the lower end of the left carotid chain in August 1979, and then disappeared over the next 2 years. The patient was hospitalized in October 1983 with needle biopsy-proven metastases to bone and was treated with 3,500 rad of radiation to the lumbar spine and sacrum. She continues on Catrix therapy. Prednisone was cancelled in October 1984. Tamoxifen citrate was begun during radiation treatment and continues at 10 mg/day. The patient is fully active and able to continue her career as a concert violinist.

Outcome. Partial response (with relapse); full activity 7 years after Catrix begun.

Case 4

M.B. was a 57-year-old woman who had a history of adenocarcinoma of the breast, treated by left radical mastectomy in March 1968. She was given radiation and chemotherapy from 1968–1970. Details of this chemotherapy could not be obtained. She then had *N, N', N'''*-triethylenethiophosphoramidate (Thiotepa) from 1972–1974, androgens and cyclophosphamide (Cytosan) (March–June 1974), and 5-fluorouracil (5-FU) and methotrexate (June 1974–September 1975). She appeared for Catrix therapy in August, 1976. At the start of Catrix therapy, the entire anterior chest wall was a field of malignant ulcers and large subcutaneous masses, both on the operated side and in the remaining breast, chemotherapy having become ineffectual. The largest ulcer was 12 cm in diameter in the region of the previous mastectomy. Despite the size of the chest lesions, there were no distant metastases except for supraclavicular and axillary nodes, both of which were grossly involved bilaterally.

Therapy Regimen

The Catrix dose regimen was 100 ml/week subcutaneously, August 1976–February 1977. From March to April 1977, she received 4.5 g/day orally; and April–July 1977, 6 g/day orally. There was no concomitant therapy. The patient died in August 1977.

Comments

There was progressive improvement on the ulcers on the left chest, which decreased from 12 cm to $5 \times 3\frac{1}{2}$ cm in diameter. There was also a reduction in the size of the mass in the right axilla, from 6 cm to $1\frac{1}{4} \times 1\frac{1}{4}$ in diameter, in August 1977, and softening of satellite nodules on the chest wall (September 1976–April 1977). A general improvement of the observable lesions continued until July 1977. Her death was due to congestive heart failure and cardiac arrest in August 1977.

Outcome. Partial response; cardiac death.

Case 5

In March 1976, O.H., a 63-year-old woman, was found to have a papillary cystadenocarcinoma of the ovary, with peritoneal and supraclavicular metastases. It could not be resected because of peritoneal carcinomatosis. She was given Melphalan, or p-di(2-chloroethyl)amino-1-phenylalanine (Alkeran) (6 mg/day, 5 days/month) from June 1976–September 1977, without effect. When she began Catrix therapy in April 1978, she had a large mass in the right pelvis (10 cm in diameter) and massive ascites. She had a partial obstruction at the level of the upper rectum.

Therapy Regimen

The Catrix dose regimen was 9 g/day orally, April–October 1978; 6 g/day orally, January–July 1979; and 4.5 g/day orally, July 1979–February 1980. There was no concomitant therapy. The patient took very little Catrix from February 1980 to September 1981. She died in February 1982.

Comments

The pelvic mass was no longer palpable by the end of April 1978, and the abdominal swelling and obvious ascites rapidly disappeared. No measurements were made of abdominal girth, but the patient stated that "her clothes all fit again." She had lost 11 lbs, which she regained within 3 months as lean body mass. A pelvic examination was normal in June 1978, and the two 1-cm hard right supraclavicular nodes had decreased in size and were barely demonstrable. These nodes disappeared entirely by August 1978. Gall bladder surgery on October 23, 1978 by the surgeon who had made the original diagnosis showed no intraperitoneal evidence of malignancy, and biopsies of the omentum, liver, and gall bladder showed no cancer.

The patient's husband suffered a massive cardiovascular accident in February 1980, and then had several myocardial infarctions, finally dying in June 1980. From the start of his illness, the patient took virtually no Catrix, and little food. Reappearance of supraclavicular nodes occurred in September 1981, with the recurrence of ascites and a pelvic mass in October of the same year. She died in February 1982. Although there is no certainty, it is difficult indeed not to associate her death with the cessation of Catrix treatments after such a superb response.

Outcome. Complete response; relapse and death following cessation of Catrix.

Case 6

M.H. was a woman of 58 when she started Catrix therapy. Her condition had been followed by a gynecologist for more than a year because of repeated Class III and IV Pap smears. There was an inflamed area around the os measuring 2 cm in diameter. A biopsy in November 1977

showed in situ cancer of the cervix. There was no evidence of extension beyond the cervix. She declined hysterectomy and radiation.

Therapy Regimen

The Catrx dose regimen was 9 g/day orally, December 1977–June 1978. From June 1978 to January 1979 the patient received 4.5 g/day orally; and 3 g/day orally, January 1979–present. There was no concomitant therapy.

Comments

The patient's Pap smear (previously Class III or IV) reverted to Class I by May 1978 and has remained so to date. Cervical biopsies showed mild dysplasia from May to August 1978. A biopsy in February 1982 proved normal, and a Pap smear on the same date was Class I. Pap smears in September 1983, February 1984, and January 1985 were Class I. The patient is in excellent general health, as of May 1, 1985.

Outcome. Complete response, probable cure (7 years).

Case 7

P.G., a 57-year-old woman, had a supracervical hysterectomy in 1973 for a leiomyosarcoma of the left broad ligament. Following this, she received 5000 rad of radiation in the pelvis through two ports. In July 1975, she developed lung metastases in the right lower lobe, which were excised by lobectomy. She developed a cervical stump recurrence plus metastases to the left posterior thigh in January 1977. She then underwent excision of the cervical stump, bilateral salpingo-oophorectomy, and wide excision of the left posterior thigh musculature. She continued to have fluid accumulation in the left thigh. Malignant cells were found in the aspirated fluid, and in tissue removed from the thigh in June 1980.

Therapy Regimen

The Catrx dose regimen was 9 g/day orally, June 1980–August 1981. The patient discontinued Catrx, August–September 1981, without consulting her physician. She restarted Catrx treatments at a dose of 9 g/day orally, September–October 1981; 2.25 g/day orally, October 1981–December 1982; and from January 1983 to the present, she is on a dosage of 9 g/day orally. There has been no concomitant therapy.

Comments

Fluid repeatedly accumulated in the left thigh, requiring drainage prior to Catrx therapy. The fluid accumulation decreased, and was absent September 1980–August 1981. Some fluid accumulation was evident, August–September 1981, but then ceased. A 2.5-cm metastatic nodule was removed from the right buttock in October 1983; histopathology revealed "evidence of immune reaction about a small collection of leiomyosarcoma cells," according to a pathologist unaware of the therapy being given. The patient continues to feel well as of May 1, 1985. Her weight has remained constant. A recent unrelated event was the passage of a right ureteral stone.

Outcome. Complete response; with relapse and ongoing second complete response (as defined); and demonstrable immune histologic response.

Case 8

L.A. is an 81-year-old man who had a carcinoma of the prostate diagnosed at a transurethral resection (TUR). He was relieved of dysuria by this procedure. He was then placed on diethyl stilbestrol (DES), 1 mg/day, in March 1976. In June 1977, while on DES, he had a firm nodule (2 cm) in the right prostatic lobe, and bone metastases were demonstrated in the right 10–12th ribs and in the pelvis. His total acid phosphatase was 22 ng/ml (high normal = 11.0 ng/

ml). Since DES was not effective, he was placed on Catrix at that time, although the DES was continued for a time at his request.

Therapy Regimen

The Catrix dose regimen began with 4.5 g/day orally, June–July 1977, and increased to 9 g/day orally, July 1977–January 1979. From January to October 1979 the dose was 4.5 g/day orally; 3 g/day orally, October 1979–May 1980; 9 g/day orally, May 1980–May 1981; 6.75 g/day orally, May–October 1981; 2.25 g/day orally, October 1981–December 1982; and 9 g/day orally, December 1982–present. The concomitant therapy was 1 mg/day DES, March 1976–December 1979; December 1979–May 1981, 1 mg DES 3 times/week for 3 of 4 weeks; and November 1983–March 1985, 1 mg DES 3 times/week.

Comments

The acid phosphatase level returned to normal by August 1978 and remained so until August 1979. The nodule was no longer palpable by March 1978. The nodule reappeared in the right lobe and acid phosphatase level rose to just above the high end of normal in May 1980. Following an increase in Catrix dosage, the nodule disappeared again by June 1980, and the acid phosphatase level returned to normal by July 1980 and remained so until November 1982. Perineal needle biopsies performed in October 1981 showed a normal prostate gland. There was a slight elevation of his acid phosphatase level in November 1982, which continued until November 1983, without palpable pathology in the prostate. DES was begun after an 18-month hiatus, with a prompt drop to normal in enzyme level, suggesting synergy, since DES had been ineffectual previously. As of May 1985, he is well, with normal acid phosphatase levels, a normal gland by palpation, and is off DES as of March 18, 1985.

Outcome. Complete response; recurrence after long period of Catrix therapy; synergy with DES.

Case 9

R.G. was a man of 60 when he developed urinary retention, and had a TUR and bilateral orchidectomy for a large carcinoma of the prostate. At the same time, bone scans showed large numbers of metastases in the pelvis, hips, spine, ribs, and clavicles, with severe pain. DES at doses of 1 mg twice a day was effective for about a year, but by November 1977 the pain had gradually returned to its former intensity. At this time, treatment with DES was cancelled and Catrix begun. Total acid phosphatase was 47.3 ng/ml at that time.

Therapy Regimen

The Catrix dose regimen was 4.5 g/day orally, October 12, 1977–February 1980; February–March 1980, 9 g/day orally; March–July 1980, 4.5 g/day orally; July 1980–October 1981, 9 g/day orally; and October–December 1981, 18 g/day orally. Concomitant therapy included 1 mg DES twice a day, May 1976–October 1977; October–December 1981, 5 mg/day of DES; and radiation (2,000 rad) to the upper thoracic spine in December 1981. The patient died in October 1983.

Comments

When Catrix therapy was begun, the patient had intense pain in the spine, pelvis, and shoulders, and his prostate gland was rock hard. His pain was virtually gone after a week of Catrix. His total acid phosphatase level, which was 47.3 ng/ml on October 6, 1977, at the start of Catrix therapy (normal ≤ 11), was 11.7 ng/ml on October 25, 1977 and normal at 6.9 ng/ml on November 16, 1977. It then remained at this level until February 1, 1981, when it rose to 19, in association with the difficulties outlined herein.

His bone scan, which had been grossly and widely abnormal, became negative after 12 days of therapy. There was progressive softening of the prostate by digital examination, until it was

normal in December 1977. Metastatic involvement of the left clavicle was found in November 1980, associated with some sporadic elevations in acid phosphatase. The Catrix dose was increased in October 1981, in response to a consistent increase in acid phosphatase. A bone scan in the same month confirmed the presence of widespread bony metastases. Cord compression at T-3 and T-4 due to subdural metastases with paraplegia required radiation treatment in December 1981. Beginning in May 1982, cycles of cyclophosphamide (Цитoфан), doxorubicin hydrochloride (Adriamycin), and cis-diaminedichloroplatinum (Platinol) were given by other doctors, without significant improvement in the patient. He died in October, 1983.

Outcome. Complete response; relapse after 3 years of Catrix; rapid progression to death despite radiation and chemotherapy.

Case 10

W.S. was a 62-year-old man when urinary symptoms led to cystoscopy and needle biopsy in October 1976, confirming the initial diagnosis of a cancer of the prostate, primarily centered in the right lobe and measuring 6 cm in diameter. Doses of DES (1 mg twice a day) for 2 months resulted in a reduction in size to 2.5 cm and a reduction in the acid phosphatase level to normal. However, he declined to take more DES, stating it was "turning him into a woman." Catrix therapy was then begun, with the acid phosphatase again elevated (20 ng/ml) and the tumor 3.0 cm in diameter. The patient had had severe asthmatic bronchitis for many years, and was on aminophylline and various aerosol bronchodilators. During Catrix therapy, he was hospitalized with pneumonia on two occasions, both requiring intubation and a respirator.

Therapy Regimen

The Catrix dose regimen was 100 ml/week subcutaneously, December 1976–March 1977; March 1977–March 1978, 3 g/day orally; March 1978–January 1979, 4.5 g/day orally; and January 1979–March 1981, 3 g/day orally. From August 1980 to March 1981, subcutaneous Catrix, at 100 ml/week, was added to the oral dose. From March 1981 to May 1982 the Catrix dose was 9 g/day orally; May–July 1982, 100 ml/week subcutaneously; July 1982–October 1983, 6 g/day orally; and 9 g/day orally from October 1983 to death. The concomitant therapy was prednisone at 10–20 mg/day (for allergies) from September 1977 to death. The patient died in January 1984.

Comments

There was a reduction in the size of the right lobe nodule to 1 cm by March 1977, but moderate enlargement occurred in the next month. The acid phosphatase level decreased rapidly and remained so until August 1980. The nodule again decreased in size, and changed position as of October 1978. There was further reduction of the nodule to normal by January 1979. Residual cancer (a few scattered cells) were found by transperineal prostatic biopsy on June 17, 1981. No mass had been palpable by examination since January 1979. Acid phosphatase was consistently normal from beginning in November 1983. The patient died suddenly at home of cardiac arrest on January 20, 1984. His asthmatic bronchitis had been well controlled at that time.

Outcome. Complete response; possible cure; cardiac death.

Case 11

W.T. was a 61-year-old man when he was diagnosed as having cancer of the prostate, which was found during a TUR for obstruction in August 1979. He declined DES, radiation, orchidectomy, or radical perineal prostatectomy as treatments for his cancer. Catrix therapy was begun in September 1979.

Therapy Regimen

The Catrix dose regimen was 9 g/day orally from September 1979 to the present; and 250–350 ml/week subcutaneously, July–November 1980. The concomitant therapy was DES 2.5

mg/week-7 mg/day, May 1981-June 1982; November-December 1983, DES 1 mg 4 times a day; December 1983-December 1984, DES 1 mg 4 times a day for 3 days; December 1984-February 1985, DES 3 mg/day; and from January 1985 to the present, Ketoconazole, starting at 900 mg/day and progressing in 1 month to 1600 mg/day.

Comments

Prostate size was unchanged (3 cm) and there was a gradual increase in acid phosphatase until July 1980. A physical examination in November 1980 showed a further slow increase in prostate size, and total acid phosphatase continued to be elevated at ~ 60 ng/ml. Bone scans were negative in September 1980 and August 1981. By the end of 1981, the prostate had become 3 times normal size and rock-hard. Total acid phosphatase was about 70 ng/ml at that time. The acid phosphatase level dropped rapidly to normal following addition of DES in November 1981 and the prostate became entirely normal to palpation.

The patient developed migratory thrombophlebitis in January 1983. This occurred concomitantly with a marked new increase in acid phosphatase, which went higher as the phlebitis grew worse. This increase took place despite an increase in DES, to 3 mg/day. Ketoconazole was therefore begun at 900 mg/day in January 1985 and slowly increased to 1,600 mg/day, with a good initial response in serum testosterone (from 280 ng/dl down to 120 ng/dl), and a sudden fall in total acid phosphatase, from 54 ng/ml the previous week to 8 ng/ml. This decrease in the enzyme occurred at the same time as the ketoconazole dosage had reached 1,600 mg/day. The right prostate nodule decreased from 4 to 1 cm in diameter and is still decreasing as of May 1, 1985. His phlebitis (and the necessity for continuing anticoagulation) also ceased at this time. The patient sought out radiation therapy despite these encouraging developments, and this treatment is currently underway against my advice, but with my full cooperation. There is no evidence that Catrix made a difference in this case but it is being continued at the patient's request. DES also failed after an initial success; ketoconazole is successful for the moment.

Outcome. No response to Catrix alone (increasing disease); responses to DES first, then to ketoconazole.

Case 12

G.D. was a 54-year-old man when a large adenocarcinoma (approximately 12 cm in diameter) filling the rectum was found, explaining persistent rectal bleeding. In addition, barium enema and colonoscopy revealed three adenomatous polyps in the transverse colon. There was no evidence of liver or nodal metastases. He declined surgery, chemotherapy, and radiation for a variety of reasons, and requested Catrix therapy. After rebiopsy of the lesion, this therapy was begun in July 1974.

Therapy Regimen

The Catrix dose regimen was 100 ml/week subcutaneously, July 1974-February 1976; February 1976-April 1977, 100 ml/month subcutaneously; April 1977-April 1980, 1.5 g/day orally; April 1980-April 1981, 9 g/day orally; and April 1981-January 1982, 6.75 g/day orally. From January to September 1982, the dose was 5.6 g/day orally; September-December 1982, 3 g/day orally; and 9 g/day orally, December 1982-present. There was no concomitant therapy.

Comments

The large carcinoma, which was without evidence of metastatic spread, was reduced to two small polyps, each with approximately 0.8-cm tips and 2-cm stalks. One polyp was still malignant on biopsy in January and March of 1975. The polyps were much reduced in size, and evidence of malignancy was found in only one on its removal in December 1975. This polyp consisted of a carcinoma in situ at the tip and a benign stalk. There was no evidence of any residual lesion by sigmoidoscopy or barium enema in February and July, 1976. Significant weight gain (20 lbs) by the patient continued. Sigmoidoscopy was normal in September 1982,

March and June 1983, and January 1984. The three polyps demonstrated by colonoscopy in the transverse colon disappeared radiographically by July 1976, and the stool continues negative for occult blood. His CEA remains less than 2.5 ng/ml. Sigmoidoscopy was again normal on May 20, 1985, and the patient is in good health.

Outcome. Complete response; probable cure (11 years).

Case 13

W.D. was a 79-year-old man in August 1977, when a cancer of the rectum was diagnosed by biopsy of a large (12 cm) rectal lesion involving the anal sphincter. He declined surgery, chemotherapy, or radiation because he had heard of the success in Case 12. No evidence of distant metastases was seen in the liver or elsewhere.

Therapy Regimen

The Catrix dose regimen was 3 g/day orally, September–October 1977; and 9 g/day orally, November 1977–May 1979. There was no concomitant therapy. The patient died in August 1979.

Comments

There was significant (10 lbs) weight gain, and an approximately 50% decrease in tumor mass was estimated by sigmoidoscopy in November 1977. An area of ulceration replaced the cancer by April 1978, and 10 biopsies between April 1978 and January 1979 were negative for malignancy. In March 1979, a left lower quadrant end-colostomy with mucus fistula was performed because of anal incontinence. The patient was discharged to a nursing home because of senility. Sudden death in the nursing home occurred in August 1979; the cause is unknown, presumably cardiac arrest.

Outcome. Complete response; possible cure; cardiac death.

Case 14

M.K. was a 50-year-old man when a carcinoma of the splenic flexure was diagnosed in July 1974, after he complained of cramps and blood in his stool. A left hemicolectomy was done for a large (24 × 15 × 15 cm) mass. Neither nodes nor liver were involved. He did well until June 1975, when a barium enema showed a recurrence, confirmed by colonoscopic biopsy on July 31, 1975, after he had bled into the gut. He declined chemotherapy and Catrix was begun.

Therapy Regimen

The Catrix dose regimen was 100 ml/week subcutaneously, August 1975–June 1976. The concomitant therapy was 5-FU for 5 days each month, August 1975–June 1976. The patient died in July 1976.

Comments

Barium enemas showed shrinkage of the tumor mass, through April 1976. Death was presumed to be due to myocardial infarction (MI) in July 1976. A postmortem showed marked generalized tumor necrosis with bleeding. There were no metastases in the liver or lymph nodes. The presence of a large fatal MI was confirmed.

Outcome. Improved response; possibly influenced by concomitant 5-FU; cardiac death.

Case 15

W.G. was a 65-year-old man who had intestinal obstructive symptoms in February 1982. A work-up revealed cancer of the hepatic flexure. At operation the cancer was found to have

invaded the anterior surface of the duodenum, and a portion of the anterior wall was removed, along with the right colon. An ileo-transverse colostomy was done. No nodes were involved. The patient recovered well, but reobstructed in October 1982. Reoperation showed an obstruction in the ileum immediately proximal to the anastomosis, and proximal to that in a jejunal loop 2 feet beyond the ligament of Treitz which was attached to the tumor site. The ileum and colon proximal and distal to the anastomosis were resected and a new ileo-colostomy was performed. The attached jejunal loop was excised and a jejuno-jejunoostomy was done. Pathology examination showed the obstruction to be due to recurrent adenocarcinoma identical to the original lesion with extension into the resection line. Again, he did well postoperatively, but after 1 month his CEA had risen to 15 ng/ml, and Catrix was begun.

Therapy Regimen

The Catrix dose regimen was 100 ml/week up to 3,000 ml, subcutaneously, November 1982–May 1983; and from May 1983 to the present, 9 g/day orally. There was no concomitant therapy.

Comments

At the start of Catrix therapy, a 5-cm mass could be felt over the duodenum, where the recurrence had been demonstrated at surgery, and the patient had cramps of considerable severity, localized to the right upper abdomen. CEA fell from 15 ng/ml at the start of therapy to 6 ng/ml by January 1984. All cramps disappeared, the mass disappeared, and he has gained 20 lbs. CEA remains at 6 ng/ml. He feels entirely well as of May 1, 1985.

Outcome. Complete response; possible cure at 2.5 years.

Case 16

A.F. was a 61-year-old man when loss of weight and anorexia led to the diagnosis of an adenocarcinoma of the stomach, in May 1975. An esophago-gastrectomy and splenectomy were performed. No nodes were involved. The patient did well in the immediate postoperative period, but mild anorexia led to diagnosis (by endoscopy and biopsy) of a recurrence at anastomosis in October 1975. Catrix therapy was then begun.

Therapy Regimen

The Catrix dose regimen was 100 ml/week subcutaneously, October 1975–April 1977; March–June 1977, 3 g/day orally; June–November 1977, 6 g/day orally; and November 1977–March 1978, oral Catrix-S at 40 ml 3 times a day. The concomitant therapy was 5-FU for 5 consecutive days each month, October 1975–July 1976 (refused thereafter). The patient died in March 1978.

Comments

By February, 1976, there was no residual evidence of cancer by endoscopy. Dysphagia and pressure in the region of the anastomosis began in March 1977, but no cancer was visible by endoscopy. Exploratory surgery in August 1977 because of continuing symptoms showed a 1–2-cm rim of cancer in the resected tissue surrounding the esophago-gastrectomy done at the original resection, and small (1 cm) left hepatic lobe metastases, as well as at least one 1-cm celiac node metastasis. He did well until January 1978 when the obstruction reoccurred. This was relieved by bouginage. Death was due to pulmonary embolus that occurred while the patient was in the hospital, in March 1978. The postmortem showed cancer in small but numerous fibrotic liver metastases, in the celiac nodes, and in a small (1 cm) fibrotic mass around the anastomotic site. The pulmonary embolus was confirmed.

The remarkable immediate therapeutic response (clearing of the esophageal recurrence) is retrospectively considered to have been a synergism between Catrix and 5-FU. In this case and in certain others the usual benefit of 5-FU alone was exceeded.

Outcome. Complete response with relapse; probable synergy with 5-FU with relapse after its cessation; death due to embolism.

Case 17

E.H. was a 73-year-old woman when she came to the office with a very large (24×12 cm) mass in the epigastrium. She had refused surgery (and any other treatment) for 1½ years after her diagnosis had been made by a gastrointestinal (GI) series and by gastroscopy with biopsy. She was so emaciated that surgery seemed precluded until metabolic improvement could be achieved. Catrix therapy therefore was begun.

Therapy Regimen

The Catrix dose regimen was 9 g/day orally, May 1977–July 1978. From July 1978 to January 1979 the oral intake was problematic and increasingly erratic, with an average of 2.25 g/day. There was no concomitant therapy. The patient died in February 1979.

Comments

Pyloric obstruction recurred, concomitant with a dramatic and progressive shrinkage of the tumor mass (from 24×12 cm to 3×3 cm diameter). A fibrotic mass was removed from the pylorus by limited Billroth I partial gastrectomy in August 1977. On pathology exam, it was found to contain rare malignant cells. There was no other demonstrable cancer in the peritoneum, and no nodes were involved. The patient was entirely normal for more than a year, and gained 18 lbs. In September 1978, Krukenberg tumors of the ovaries were removed, one demonstrating cancer, the other necrosis. A pelvic mass was evident on examination in December 1978; presumptive liver metastases were seen by liver scan, and recurrent carcinoma of the efferent loop of the gastro-jejunostomy was seen by GI series at this time. She died at home in February 1979. As noted, from July 1978 onward, she was probably not on effective Catrix dosage. This was due in part to her residence at a health farm that substituted coffee enemas, megavitamins, and pancreatic enzymes for her previous treatment.

Outcome. Complete response; relapse after Catrix discontinued.

Case 18

E.M. was a 63-year-old man when he was operated upon for jaundice. An adenocarcinoma of the head of the pancreas was found, with involvement of the regional nodes and liver metastases. A cholecysto-jejunostomy was done with good immediate postoperative recovery. No other therapy was recommended by his physicians. He began to lose weight at an accelerating rate, and was referred to a trial of Catrix therapy by a former patient. This therapy began in May 1977. At this time there was a large mass (~20 cm) palpable in the right upper quadrant (RUQ) and a high alkaline phosphatase (300 with high normal of 150 mu/ml).

Therapy Regimen

The Catrix dose regimen was 6 g/day orally, May–December 1977; and 9 g/day orally, December 1977–October 1978. There was no concomitant therapy. The patient died in October 1978.

Comments

The palpable mass disappeared by September 1977. A reduction in size of the hepatic metastases was evident by ultrasonography and computed tomography (CT) scanning. The alkaline phosphatase level decreased 75%. CEA levels fell from the 34–45 ng/ml range to about 15 ng/ml, and remained there until August 31, 1978. An abscess at the site of the original tumor drained 900 ml of pus in July 1978. Death in October 1978 was due to progressive respiratory failure secondary to pneumonia in the hospital where his surgery had been done.

His treatment consisted of morphine around the clock, because he was considered to be terminal. It is open to question whether this was compassionate treatment, and there is no question whatever that it is not the preferred treatment for pneumonia. In any event, the patient had survived 17 months with widespread intraabdominal metastatic pancreatic cancer, an unlikely outcome at the start of treatment. An isotopic liver scan had been negative for the first time, earlier in the month of his death.

Outcome. Partial response; demonstrated shrinkage of primary tumor and liver metastases; death due to untreated pneumonia.

Case 19

M.G. was a 60-year-old woman who had very severe cervical arthritis with constant, radiating pain requiring narcotics. She was referred by her orthopedist for Catrix treatment of her arthritis (12). She had had virtually complete relief from the schedule of dosage noted herein, but a radiologist had interpreted two sets of films as showing a diminishing of her osteophytes at the conclusion of treatment. By June 1977, her improvement was such that Catrix was discontinued. She called in January 1978, stating that she was in great pain in the RUQ. Examination showed her liver to occupy all of the right side of her abdomen to the level of the pelvis. Needle biopsy revealed adenocarcinoma consistent with pancreatic origin, and a CT scan confirmed the presence of a pancreatic mass.

Therapy Regimen

The Catrix dose regimen was 100 ml/week subcutaneously, September 1976–February 1977; February–June 1977, 4.5 g/day orally; April–June 1977, 100 ml/week subcutaneously; and February–July 1978, 9 g/day orally. There was no concomitant therapy. The patient died in July 1978.

Comments

There was a rapid decrease in the size of the patient's liver, which had filled her entire right abdomen to the iliac crest, from February to April 1978, until it was no longer palpable. Transient ascites were observed in April, 1978, and the jaundice and liver chemistries improved by May 1978. However, moderate ascites and jaundice remained and worsened again in June 1978. Her death in July 1978 was due to liver failure. On postmortem, no gross evidence of residual cancer was observed in the pancreas or elsewhere. Microscopic foci were detected in the liver and pulmonary lymphatics. I have classified this as a complete response because it is evident that the major clinical problem was the rejection of the tumor, which was too rapid and inflammatory.

Outcome. Complete response; death due to tumor necrosis in liver, with hepatic functional failure.

Case 20

P.A. was a 69-year-old woman who had surgery (at another hospital) for jaundice and a carcinoma of the head of the pancreas with nodal involvement. A Whipple procedure was done, but microscopic sections showed a transection of the cancer on the common duct. She refused chemotherapy and requested Catrix therapy.

Therapy Regimen

The Catrix dose regimen was 3 g/day orally, March–April 1977; 4.5 g/day orally, April–December 1977; 6 g/day orally, December 1977–February 1978; 9 g/day orally, February–September 1978; 6 g/day orally, September 1978–January 1979; and 3 g/day orally, January 1979 to the present. There was no concomitant therapy.

Comments

The patient's alkaline phosphatase level increased sharply to 10 times normal, from June 1977 to October 1977, finally reaching normal in May 1979. Her weight has increased steadily from 106 lbs, in March 1977, to 136 lbs in 1979, where it remains as of May 1985. Physical examination and blood chemistries are normal (May 1, 1985), and she continues to feel well.

Outcome. Complete response: probable cure (8 years).

Case 21

J.P. was a man of 45 years when a squamous cell carcinoma of the right upper lobe of the lung was diagnosed in January 1977. A right upper lobectomy was done despite demonstrable invasion of the apical pleura. Ten thousand rad of radiation was given through three ports; however, it was effective only briefly. This was rapidly followed in September 1977 by invasion of the brachial plexus and the right transverse processes of the spine at C-6 and C-7. Methotrexate, doxorubicin hydrochloride (Adriamycin), and cyclophosphamide (Cytosan) were given from February 1978 to May 1979, with some initial regression followed by a rapid resumption of growth and marked increase in pain and dysfunction of the arm secondary to brachial plexus involvement. Finally, cis-diaminedichloroplatinum (Platinol) was given, from May to September, 1979, without noticeable effect. His right arm became virtually useless due to median and ulnar nerve involvement in the plexus, and he had severe pain radiating down the arm as well as in the upper right chest and in the supraclavicular space. Catix therapy was started in May 1980.

Therapy Regimen

The Catix dose regimen was 9 g/day orally, May–December 1980; and 100 ml/week subcutaneously, June–December 1980. There was no concomitant therapy. The patient died in January 1981.

Comments

The severe pain in the right chest decreased markedly. A CT scan in August 1980 showed less prominence (~50%) of the apical mass in the right chest. There was no radiologic improvement in the degree of destruction in the C-6 and C-7 transverse processes and vertebral bodies. Ataxia and leg pain began in December 1980, due to pressure of the tumor on the spinal cord at the lowest cervical level, demonstrated by myelography. This occurred despite better arm function and lessening pain in the chest and arm. Exploration of the brachial plexus and vertebral bodies with multiple biopsies showed no remaining cancer in the entire area of the original tumor. However, laminectomy showed a subdural fibrotic mass in which a few cancer cells were seen microscopically. There was excellent improvement in leg function. However, 5 days after discharge, the neurologic signs returned, and reexploration revealed a subdural clot. He died suddenly (cause undetermined) on the evening of the first preoperative day (January 1981).

Outcome. Partial response; demonstrated absence of cancer in original sites; death secondary to neurological and operative sequelae of fibrotic contracture of subdural metastases.

Case 22

J.P. was a 63-year-old retired man in August 1976 when a squamous cell carcinoma of the lung was diagnosed by bronchoscopic biopsy. At operation, an inoperable cancer of the left lower lobe was found with very large mediastinal involvement. Radiation therapy was given from October to December 1978, totaling 6000 rad through two ports, with an excellent initial effect (disappearance of mass by film). Following its completion, Catix treatment began.

Therapy Regimen

The Catrix dose regimen was 9 g/day orally, December 1978–April 1981. The concomitant therapy was radiation to the right mediastinum (3,000 rad in 10 doses), April–June 1980. The patient died in April 1981.

Comments

Chest films following radiation therapy in December 1978 showed disappearance of the cancer with residual strand densities. Radiographs remained unchanged until April 1979, when an increase in lung mass was evident. Further increase in left lung mass was noted in May 1979, and then markedly decreased in September 1979. A tender, palpable 2 cm node, with esophageal compression, was evident at the base of the right neck by April 1980. This was treated by radiation, as noted above, with elimination of the mass and dysphagia. Films in May and July 1980 showed continuing shrinkage of the lung mass and disappearance of the esophageal compression. The patient did well until the onset of viral pneumonitis in March 1981. He was admitted to the hospital where the diagnosis had been made, and sedated rather than treated, at the request of the family. He was signed out by his local physicians as having died from pneumonia, not cancer.

Outcome. Partial response; relapse in mediastinum after 1½ years. Responded to radiation; death due to untreated pneumonia 2½ years after Catrix begun.

Case 23

M. McD, a 73-year-old man, was diagnosed as having a squamous cell carcinoma of the lung (left upper lobe). The diagnosis was made by bronchoscopic biopsy (April 1975). Although the tumor was small and without evidence of metastasis, he had such severe chronic pulmonary insufficiency that an operation could not be done. He was a heavy smoker. Radiation was contraindicated for the same reason. His sputum cytology was Class V at this time. In the absence of therapeutic alternative, Catrix therapy was begun in May 1975.

Therapy Regimen

The Catrix dose regimen was 100 ml/week subcutaneously, May–July 1975; July 1975–March 1977, 100 ml subcutaneously twice weekly; March 1977–June 1979, 3 g/day orally; and June–August 1979, 6 g/day orally. There was no concomitant therapy. The patient died in November 1979.

Comments

The patient gained 10 lbs by March 1977, and the sputum cytology was Class III. The cytology was negative (Class I or II) by November 1977 and continued to be so. CEA began to rise in September 1978 and his weight began to fall from its peak of a 20 lb gain (in June 1978) from the start of therapy. There were drinking bouts and less compliance with Catrix dosage during this period. A bronchoscopy in August 1979 showed no evidence of tumor and a negative sputum cytology. However, a CT scan of the liver at that time showed multiple liver metastases, consistent with an increase in alkaline phosphatase, which began in June 1979 and continued to increase thereafter. Sudden death occurred in November 1979 (presumably cardiac) in a nursing home where he had been placed by his family, who would not care for him or bring him for treatment, in September 1979, following bronchoscopy.

Outcome. Complete response; relapse and death 4½ years after diagnosis made.

Case 24

A.H. was a 71-year-old man in June 1975 when he was diagnosed by bronchoscopic biopsy as having squamous carcinoma of the right upper lobe of the lung. He declined surgery; therefore 5,000 rad was given through two ports, with disappearance of the lesion by bron-

choscopy. The patient was a pentobarbital addict and an incessant cigarette smoker. Sputum cytology was Class V. Catrx therapy began in August 1975.

Therapy Regimen

The Catrx dose regimen was 100 ml/week subcutaneously, August 1975–April 1976; and 100 ml, subcutaneously over 2 weeks, June–August 1976. There was no concomitant therapy. The patient died in December 1976.

Comments

Radiation therapy in July 1975 resulted in a reduction of the lesion to fibrotic streaks on follow-up radiographs. Radiographs taken in October 1975 and January 1976 showed no reappearance of the cancer. In August 1976, radiographs and sputum cytology examination were both negative (Class I), and chest films were again negative in December 1976. The patient's death in December 1976, without evidence of recurrent disease, was due to a pentobarbital overdose (he had a long history of drug abuse). The period of freedom from recurrent disease (16 months) exceeds the usual response to radiation alone, which gives about 35% survival at 17 months (~5% at 5 years).

Outcome. Complete response; possible cure; possible synergy with radiation; death due to pentobarbital overdose.

Case 25

C.R. was an 82-year-old woman when she was referred for treatment of two large basal cell carcinomas of the lumbar area that had been inadequately excised a number of times, and had failed to respond to 6000 rad of radiation therapy. The larger lesion was on the right side and was 15 × 12 cm, while the smaller was on the left and was 12 × 10 cm. She refused radical excision. Catrx therapy began in January 1978.

Therapy Regimen

The Catrx dose regimen was 6 g/day orally, January 1978–January 1979; Catrx cream applied topically, March 1978; 3 g/day orally, January–August 1979; 2.25 g/day orally, August–December 1979; 3 g/day orally, December 1979–August 1980; 9 g/day orally, August–September 1980; 100 ml/week, subcutaneous, locally, August 1980–May 1981; 3 g/day orally, September 1980–March 1981; and 9 g/day orally March 1981–October 1983. There was no concomitant therapy. The patient died in October 1983.

Comments

Steady improvement was noted in the two basal cell lesions. In May 1978 there was increased inflammation in both lesions. The smaller lesion healed in June 1978, without subsequent recurrence. The larger tumor decreased in size from August 1980 to May 1981 with increasing necrosis; subsequent epithelialization was extensive by January 1982. Sequential biopsies showed reduction in the amount of basal cell cancer present from about 20% to scattered islands, but

FIG. 1. Case 25: The ulcerated right-sided basal cell cancer after 5 months of therapy. The left lesion is healed.

FIG. 2. Case 25: The situation 5 years later. The left lesion shows radiation dermatitis, but remains healed. The right lesion is incompletely healed, but improved.

FIG. 3. Case 26: The size of the lesion in December 1976.

FIG. 4. Case 26: The situation almost 6 years later. The lesion is mostly covered with epithelium from successful pinch grafts. Much improved, but incompletely healed.

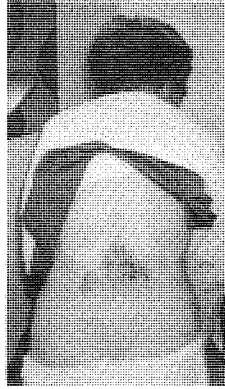
FIG. 5 a,b. Case 27: Two views of the nose in June 1980, showing malignant squamous cell cancer ulcers and nodules.

FIG. 6 a,b. Case 27: Similar views of the nose in May 1985. The red nodule on the left proved to be a presumptively de novo basal cell carcinoma on biopsy (see herein).

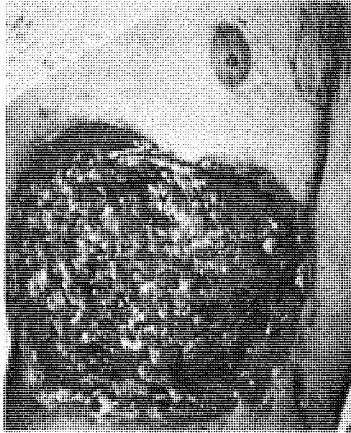
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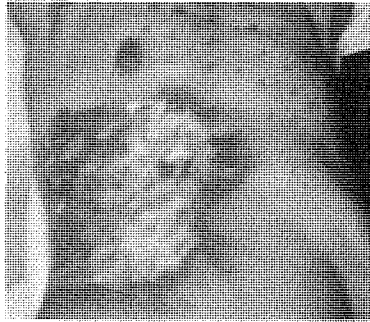
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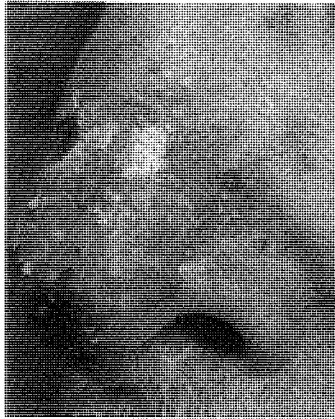
4.



5a.



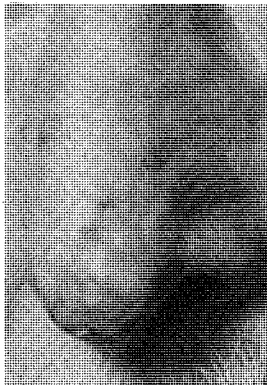
5b.



6a.



6b.



it was never completely eliminated. This led to a discussion of an excision of the now smaller lesion with closure by flap advancement. This the patient refused. Figures 1 and 2 show the healing which was achieved between March 1978 and May 1983. Increased problems in taking care of herself at advanced age (87) led to malnutrition. Death occurred at another institution in October 1983 due to viral pneumonia. This was almost 6 years after she had been referred to me for rapidly advancing cancers unaffected by any available therapy.

Outcome. Partial response; death due to viral pneumonia at age 87.

Case 26

F.V., a 59-year-old man, came for treatment of a huge (30 cm in diameter) neglected basal cell carcinoma of the right side. This carcinoma was invading the ribs, causing collapse of the lower anterior chest wall, and had invaded and destroyed the right abdominal wall to the peritoneal level in several areas (Fig. 3). He was a severe congenital athetotic and very slight of build. He was a recluse due to his athetosis, and had allowed the tumor to grow to its enormous size over more than 5 years before reporting it. Because of that and because of the extent of the lesion, an operation was considered out of the question. In the 3 months preceding the start of Catrix therapy, 9,000 rad had been given through three ports with no discernible effect. Catrix treatment began in December 1976.

Therapy Regimen

The Catrix dose regimen was 100 ml/week subcutaneously, December 1–31, 1976; January 1–July 31, 1977, topical powder at 1 g/cm²/week; July–December 1977, Catrix-S at 120 ml/day; December 1977–March 1978, Catrix-S at 180 ml/day; March–April 1978, 4.5 g/day orally; April 1978–January 1983, 9 g/day orally; and July 1980–February 1981, 100 ml/week, subcutaneous, locally. There was no concomitant therapy. The patient died in March 1983.

Comments

The patient's general condition improved, but cancer was still present by repeated biopsy from December 1976 through January 1979. By January 1979, lesion size was reduced by 30%. From January 1979 to July 1980, there was a gradual filling in of granulation tissue, but progress halted in July 1980. Subcutaneous Catrix injections at the site from July 1980 to February 1981 promoted granulation tissue growth. Pinch grafts in February 1981 were highly successful initially, but gradually were lost. By June 1982, no cancer was demonstrable by biopsy, although the patient weighed only 85 lbs. His family, wearying of his care, consulted a cancer center, which planned an excision of the entire right chest wall and abdominal wall with replacement. He was admitted for this over protest by both myself and the patient. He was so frightened by this prospect that he died in March 1983 of a gastric ulcer hemorrhage the night before the operation. This was 7 years after he had been referred for the enormous lesion shown in Fig. 3, for which he was thought to be terminally ill at that time. Figure 4 shows the improvement in the lesion achieved over time, as well as the size of the lesion which remained. As previously noted, the last biopsy, in June 1982, showed no cancer cells in the specimen.

Outcome. Partial response; continual slow improvement; death due to gastric hemorrhage.

Case 27

D.G., a retired doctor, was 79 when he came for Catrix therapy for a widespread squamous carcinoma of the nose, for which three consultants had recommended excision of the nose. The cancer was thought possibly to have been caused by the patient's frequent use of the fluoroscope in his office. There were no other lesions on his face, and there were no cervical nodes. He refused excision of his nose because of the disfigurement, electing to try conservative treatment. Catrix was begun in June 1980. At that time, the nose exhibited multiple nodules and at least five small malignant ulcers which bled frequently (Fig. 5).

Therapy Regimen

The Catrix dose regimen was 9 g/day orally, June 1980–present; June–August 1980, 10 ml/week, subcutaneous, locally, 3 weeks/month (total dose locally = 100 ml); June 1980–present, 5% Catrix cream applied locally twice a day; and August–December 1980, 100 ml/week subcutaneously. There was no concomitant therapy.

Comments

Considerable improvement was found as of January 1981, with further improvement noted to date. The nose is currently (May 1, 1985) smooth-textured by palpation and inspection (Fig. 6), with some scarring where the previous cancer ulcers had been. The patient is in good general health, and there are no metastases.

A recent biopsy of both sides of the nose at points where the largest nodules had been showed actinic dermatitis on the right and a small basal cell carcinoma on the left. The latter may represent a differentiation of the original squamous cell carcinoma, or more likely, a new lesion arising in the radiated area. A course of weekly direct injections of 2 ml of 5% Catrix-S into both sides of the nose has been started. This course will last 6 weeks.

Outcome. Complete response; probable cure (5 years after excision of nose strongly advised).

Case 28

F.P. was a young man, age 21, when he came for Catrix treatment because of a large upper mediastinal mass and a supraclavicular node on the right. The mass occupied fully 50% of the transverse diameter of the chest at the level of the 3rd sternal-chondral junction. A biopsy elsewhere had shown the microscopic characteristics of Hodgkin's disease with mixed cellularity. He refused radiation and/or chemotherapy, both of which were strongly recommended. Catrix was therefore begun in September 1977.

Therapy Regimen

The Catrix dose regimen was 3 g/day orally, September–October 1977; October–November 1977, 4.5 g/day orally; November 1977–September 1978, 9 g/day orally; October 1978–May 1979, 13.5 g/day orally; December 1979–April 1980, 9 g/day orally; April–May 1980, 4.5 g/day orally; May–August 1980, 9 g/day orally; and August 1980–May 1983, 6 g/day orally. The concomitant therapy was Mustargen, Oncovin, prednisone, and procarbazine (MOPP), and radiation to the mediastinum, June 1979–May 1980.

Comments

There was stabilization of the mediastinal mass through June 1979 (almost 2 years). Liver, spleen, and abdominal nodes were normal by CT scan, and have remained so. The patient accepted radiation and chemotherapy in June 1979, and the mediastinal mass decreased by 75% by October 1979. The mass continued to decrease through May 1983, at which time only about 5% of its former bulk remained. He discontinued Catrix against advice in May 1983. Catrix alone stabilized this tumor for almost 2 years, but did not reduce it (possible steady state). This tumor is much bigger than those followed by Crafts and reported by DeVita (36), in which about 80% of the patients were dead 21 months after diagnosis. Twenty-one months was the interval of no change in tumor size or health in this patient, using Catrix therapy. He is in good health as of May 1, 1985.

Outcome. No change; chemotherapy required to reduce mass after 2 years stabilization.

Case 29

D.W. was a 79-year-old woman when she was started on Catrix therapy. She had had a right nephrectomy in January 1976 because of a renal cell carcinoma. Lung metastases then occurred, and were thought to be confined to the left upper lobe. A left upper lobectomy was therefore

done in August 1976. There were multiple metastases in the specimen, indicating their presence elsewhere. Multiple lung metastases appeared in May 1978, together with a large liver mass in the right lobe by CT scan. Catrx therapy was then begun.

Therapy Regimen

The Catrx dose regimen was 9 g/day orally, October 1978–September 1979. There was no concomitant therapy. The patient died in February 1980.

Comments

There was a radiologically-documented progressive decrease in the lung metastases, until they were no longer discernible on chest films in September 1979. The patient gained strength and weight (10 lbs), until she suffered a stroke with a left hemiparesis in September 1979. A CT scan in November 1979 showed a large metastasis in the right lobe of the liver. Her death in February 1980 was due to hemorrhage and peritonitis secondary to the rupture of a large necrotic liver metastasis into the peritoneum. This event had been unrecognized and untreated in a nursing home. The autopsy showed a large amount of hemorrhagic necrotic material in the right hepatic lobe, peritonitis, pneumonitis, and no residual demonstrable cancer, grossly or microscopically.

Outcome. Complete response; probable cure; death due to peritonitis.

Case 30

E.S. was a 59-year-old woman when she was started on Catrx treatments. She had had a convulsion while on a trip in California and had been operated upon for a brain tumor in the right frontal lobe. An incomplete excision had shown a glioblastoma multiforme (Grade IV), and direct invasion of the skull was seen. She recovered well initially, and received 600 rad of radiation before she refused further treatment because of hair loss. She declined chemotherapy after she read up on the results. A baseline CT scan showed the lesion occupying most of the right frontal lobe. Catrx was begun in June 1978.

Therapy Regimen

The Catrx dose regimen was 9 g/day orally, June 1978–December 1979; and 4.5 g/day orally, December 1979–September 1981. There was no concomitant therapy.

Comments

Consecutive CT scans showed a progressive decrease in tumor size. By April 1979, there was no evidence of residual neoplasm by CT scan, and there has been no recurrence. The patient discontinued therapy against advice in September 1981. At last contact May 1985, she is entirely well.

Outcome. Complete response; probable cure (7 years).

Case 31

M.C. was a 59-year-old woman who had had a total thyroidectomy for a medullary carcinoma of the thyroid, followed by a right radical neck dissection and mediastinal dissection along the innominate artery. There was cancer below this point at surgery, and a mass later appeared alongside the trachea in follow-up chest films, extending downward to the right main stem bronchus. A bone scan showed metastases in the right fourth rib and in the right clavicular head. Her weight declined from 125 lbs to 106 lbs, and her energy decreased. Her calcitonin preoperatively was 9,710 pg/ml, and fell postoperatively to 1,700 pg/ml. However, it promptly began to rise, and reached 16,000 pg/ml at her initial treatment with Catrx in September 1982. Severe diarrhea had developed as the mediastinal tumor increased. She had declined radiation and chemotherapy because of the reported low response rates and lack of reported

cures. Initial measurement of the tumor on chest film was 7×2.3 cm. She was maintained on daily 0.2 mg levothyroxine sodium (Synthroid). Three to four diphenoxylate hydrochloride with atropine sulfate (Lomotil) and mepenzolate bromide (Cantril) per day were necessary to control diarrhea.

Therapy Regimen

The Catrix dose regimen was 9 g/day orally, September 1982–present. There was no concomitant therapy.

Comments

There was a gradual 10-lb gain in weight (to 116 lbs) in May 1984, and a decrease in serum calcitonin, from a peak of 16,000 to 6000 pg/ml. The size of the mediastinal mass decreased from 7×2.3 cm to 3.5×1.0 cm in May 1984 (80% cross-sectional reduction). At the start of treatment, she had severe diarrhea, necessitating the medications listed previously. Now she is off the Cantril and needs only one or two Lomotils per day. She shifted her Catrix dosage without permission in March 1984 from eight capsules (3 g) 3 times a day to 9 grams in one dose. Because of her residual diarrhea, this was almost certainly a de facto reduction of dosage because of loss in the stool. Concomitantly, her calcitonin level has risen to 9,600 pg/ml, yet the CEA has fallen from 64 to 32 ng/ml. She has just begun to take the Catrix in the original dosage pattern. The clavicular head size has not decreased, but there is now no pain. She plays tennis and is fully active.

Outcome. Partial response; relapse probably related to dosage noncompliance.

DISCUSSION

Catrix has been shown to exert a major inhibitory effect upon a wide spectrum of cancers. The cases treated have been followed for extended periods, the longest being 11 years. Of all of these reported, the one considered most certainly to have been cured is the glioblastoma patient reported in Case 30. She remains well 5 years after cessation of Catrix against my advice. In addition, there are a number of cases which give every evidence of cure; but the patients are still on Catrix, and, in a few cases, the reappearance of the cancer when the medication was stopped makes me cautious regarding the final categorization of these cases (see herein).

The case histories indicate that Catrix has capacity to arrest the growth of many cancers, although not necessarily to eliminate them immediately. For example, there are two patients (Cases 8 and 9) whose cancers of the prostate had been undetectable for 6 and 3 years, respectively, during continuous oral Catrix administration, but the cancer slowly began to escape control. This was evidenced in one case by rising acid phosphatase levels and in the other by the appearance of bone and subdural metastases, as well as an increase in the enzyme level. In one of the two cases, this reappearance was easily controlled by an increase in Catrix dosage (Case 8), and in the other the cancer was not inhibited by cancellation of the Catrix therapy and a shift to vigorous chemotherapy.

A patient with a breast cancer (Case 3) that had been inactive for more than 5 years on oral Catrix (after having remitted on that therapy from metastatic involvement of the entire axial skeleton) was recently found to have a painful, histologically-proven recurrence of the cancer in the lumbar spine, after a long period of normal activity as a concert violinist. Fortunately, the pain has been relieved by local radiation and the patient is now receiving another subcutaneous load of Catrix-S. On this therapy, her CEA has decreased from ~ 65 ng/ml to ~ 9 ng/ml over a month interval, her

serum proteins and hemoglobin are rising, and her sense of well-being has returned. This patient was started on Tamoxifen citrate by another physician, and this may have been of benefit. If so, it has been long-lasting, at 1.5 years.

Case 5 provides a striking example of how failure to take the Catrix due to important negative psychological events can convert a spectacular triumph into overwhelming recurrence and death. Such observations would appear to indicate that Catrix establishes a steady state without immediate elimination of the capacity to form new cancer tissue upon discontinuation of Catrix.

The series of case reports contains a number of instances where patients are without any evidence of disease as they continue on Catrix oral therapy. These include a patient with cancer of the cervix (Case 6), now 7½ years without a recurrence; a pancreatic carcinoma patient (Case 20), 8 years without recurrence; and a patient with squamous cell cancer of the nose (Case 27), 5 years without a recurrence. These presumptive cures (including the glioblastoma multiforme) constitute 13% of this unfavorable cancer population.

In addition, dramatic initial and long-term effects with eventual death due to intercurrent disease were seen in Cases 1, 2, 4, 10, 13, 14, 18, 21–26, and 29. This group represents 45% of the total.

Cases 5, 9, 16, 17, and 19 had excellent initial responses but died of their cancers due (with one exception) to compliance failures for the variety of reasons outlined in the summaries. The exception was Case 19, in which the metastatic tumor in the liver necrosed so rapidly that the patient died of liver failure. These cases constitute 17% of the study population.

Cases 3, 7, 8, 11, 15, 28, and 31 are alive, with some evidence of disease activity, but generally improving. This situation involves 23% of the study group.

This initial experience with Catrix therapy for a wide spectrum of cancers is therefore highly encouraging. Only one (Case 11), a patient with carcinoma of the prostate, failed to respond (3% of total). Five and a half years after diagnosis, he was entirely without chemical or physical evidence of cancer on standard Catrix oral dosage (9 g/day) and 1 mg DES 3 times a week. The onset of persistent thrombophlebitis has recently forced the elimination of the DES and substitution of ketaconazole with marked improvement. The response to both of these agents has suggested synergy with Catrix.

This possible hormonal synergy raises the question of synergy with other hormones, possible protection of the immune system from chemotherapeutic damage, and/or Catrix synergy with these agents. It seems unlikely that this activity, if indeed present, would be limited to one hormone or agent. Appropriate further investigation of this interaction has begun.

After consultation with several biostatistical experts, it was advised that the circumstances were too complex to permit a statistical statement of the probability that these results could have been achieved through chance selection. One expert believed that such a result is impossible on inspection, but it is likewise impossible to pretend to a precision which cannot be obtained by statistical maneuvers.

There are certain cases I have reported that are particularly striking, and whose results are indeed impossible by chance selection. These are, in my opinion, cases 1, 5, 7, 8, 12, 13, 15, 17, 19, 20, 21, 26, 27, 29, and 30. These constitute almost half of those reported. As already noted, only one (Case 11) showed no response. Therefore, all those not specifically cited showed definite responses of varying degree.

The classification of responses was as follows (see definitions for categories at start of patient summaries):

1. Complete response with probable or possible cure—11 (including special circumstances in Cases 19 and 29) (35%)
2. Complete response with relapse—8 (26%)
3. Partial response—6 (19%)
4. Partial response with documented relapse—3 (10%)
5. Improved response—1 (3%)
6. No change—1 (3%)
7. Progression—1 (3%)

Controlled studies are beginning in the United States and West Germany. At present, the policy is to use Catrix when the patient has failed to respond to all standard therapy, or has a cancer for which current therapy is generally recognized as ineffective. In order for Catrix (or any agent for that matter) to have a reasonable chance to produce convincing therapeutic responses, treatment must be commenced as soon as these conditions are met. Catrix appears to possess both antimetabolic and immunostimulatory biological efficacy; however, it will not resurrect a physiologically terminal patient, since its action depends upon there being enough biology still going on for it to modify.

When confronted by entities such as pancreatic cancer, squamous or adenocarcinoma of the lung, glioblastoma multiforme, and other situations where present therapeutic impotence is clear, the use of Catrix therapy as the primary agent should be considered. One persuasive argument for using it in this way is that, in happy contrast to chemotherapy, it burns no immunological or hematological bridges.

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