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Evaluation of Tamoxifen Doses With and Without Fluoxymesterone in Advanced Breast Cancer

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From a group of 108 female patients with measurable and/or evaluable metastatic breast carcinoma, 52 were randomized to receive tamoxifen and 56 to receive tamoxifen and fluoxymesterone. The fluoxymesterone dose, given orally twice a day, was 7 mg/m² body surface area. The tamoxifen dose per patient, also given orally twice a day, ranged from 2 to 100 mg/m² body surface area. Eighty-five percent of the patients had received previous chemotherapy and 60% previous hormone therapy. The complete and partial remission rate was better with the tamoxifen and fluoxymesterone regimen ($p = 0.016$), with remission rates of 15% for tamoxifen alone and 38% for the combination. The tamoxifen and fluoxymesterone regimen appeared to have higher remission rates in all subsets of pretreatment variables. Duration of remission with each regimen was similar, but the overall time to treatment failure for tamoxifen and fluoxymesterone was longer than for tamoxifen alone (180 versus 64 days, $p = 0.01$). Median survival with the combination was 380 days compared to 330 days for tamoxifen. No significant dose-response relationships emerged. Side effects were not different between dose levels or regimens except for the androgen effects in the tamoxifen and fluoxymesterone combination. These results suggest that there is no major dose-response effect for doses ranging from 2 to 100 mg/m² body surface area given twice daily in this largely (94%) postmenopausal pretreated patient group, and that the tamoxifen and fluoxymesterone regimen is superior to tamoxifen alone.

THE FIRST CLINICAL results with nonsteroidal anti-estrogen therapy in breast cancer were reported in 1959 (1). Subsequently, initial results with the newly developed nonsteroidal anti-estrogen tamoxifen, the *trans* isomer of 1-(p-β-dimethylaminoethoxyphenyl)-1,2-diphenyl-1-but-1-ene citrate, were reported in 1971 (2). Initial clinical trials suggested that tamoxifen was as active an antitumor agent as estrogen analogs with less or equivalent toxicity (2-4). This view has more recently been supported by the results of a comparative trial (5). Since the early reports tamoxifen has had widespread use as a single agent and has more recently been successfully incorporated into combination chemotherapy regimens (6). The usual dosage of tamoxifen ranges from 10 to 20 mg twice daily, yet no information from randomized trials is available on dose-related effects. We report our experience with doses of tamoxifen ranging from 2 to 100 mg/m² body surface area twice daily with or without the simultaneous administration of fluoxymesterone. The administration of concomitant fluoxymesterone was originally related to the observation that some patients' tumors contained androgen-receptor activity (7). These early data suggested that the two agents combined might be superior to tamoxifen alone.

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Materials and Methods

Female patients with breast carcinoma shown by biopsy results, and progressive metastatic disease were eligible for the study. Patients excluded from the study included those with organ dysfunction unrelated to tumor, other previous cancers, previous exposure to anti-estrogens or androgens, a Karnofsky performance index less than or equal to 30, or nonmeasurable and nonevaluable disease such as mixed osteoblastic and osteolytic disease or pleural effusions as the sole manifestation of disease. Informed consent was obtained from all patients.

Patients were first stratified by the dominant disease's site of involvement (visceral, osseous, or soft tissue); number of involved organ sites (fewer than or two versus more than two); measurable versus evaluable disease as defined elsewhere (8); and previous response to hormonal therapy (yes versus no versus unknown or no exposure). Patients with no previous hormone exposure or an unknown response to previous hormone therapy were also stratified by estrogen receptor status as positive, negative, or unknown; estrogen receptor assays were generally done using a competitive protein-binding assay (7). Patients were then randomized to receive treatment with tamoxifen or with tamoxifen and fluoxymesterone by a previously described technique (9).

The dosage of fluoxymesterone was 7 mg/m² body surface area, given orally twice daily. At the beginning of the trial the tamoxifen dose was 2 mg/m² body surface area, also given orally twice daily. The dose of tamoxifen for every fourth patient was sequentially increased to 4, 8, 16, 32, 50, 60, 80 and 100 mg/m² body surface area twice daily. When three patients reached a dose of 100 mg/m² body surface area, given twice daily, the dose sequencing was reversed to provide three evaluable entries on tamoxifen alone at each dose level except 50 mg/m² body surface area twice daily. Subsequently the randomization was adjusted to include the tamoxifen dose in addition to the treatment regimen. Due to the results of an early interim analysis (10) the dosing aspect of the randomization was skewed slightly in favor of the lower doses. The dose level for each patient on entering the trial was maintained until she had disease progression or relapse.

Patients were evaluated before therapy and at 1 to 3 month intervals by physical examination; history; blood cell counts;

Table 1. Response Rates to Tamoxifen and to Tamoxifen and Fluoxymesterone* †

Regimen	Patients	CR	PR	IMP	NC	PD
	n	←		%		→
Tamoxifen	52	0	15	10	25	50
Tamoxifen and fluoxymesterone	56	5	32	12	25	25

* CR = complete remission; PR = partial remission; IMP = improvement; NC = no change; PD = progressive disease.
† Overall trend, $p = 0.0025$; CR + PR, $p = 0.016$; CR + PR + IMP, $p = 0.013$.

liver and renal function tests; chest and skeletal roentgenograms; and bone, liver, and brain scintigraphic scans. During the first 2 months of therapy the patients were evaluated every 1 to 2 weeks by history, physical examination, blood counts, and liver function tests.

The response criteria used are summarized below and were similar to published guidelines (8) with the modifications previously detailed. (11). A complete remission was defined as a complete elimination of demonstrable disease for at least 4 weeks. A partial remission was a 50% to 99% reduction in the sum of the longest bidimensional perpendicular products, a 30% to 99% reduction in unidimensional measurements, or a 50% to 99% reduction in evaluable disease parameters (such as lymphangiitic pulmonary disease or partial recalcification of lytic osseous lesions) in at least 50% of the involved organ sites for at least 4 weeks. Improvement was defined for only osseous involvement as an objective lack of change associated with an osseous disease-related 20-point improvement in Karnofsky performance index or marked reduction in analgesic requirements lasting at least 8 weeks. This definition was previously suggested to be the same as a partial remission with respect to the duration of disease control in a chemotherapy trial (11).

Patients never achieving a complete or partial remission, improvement, or progressive disease status were classified as having no change. Progressive disease was defined as the appearance of any new lesion, a 50% or greater worsening of evaluable involvement, or a 25% or greater increase in the measurements of the lesions in any organ site as long as the increase was at least 2 cm^2 for bidimensionally or 2 cm for unidimensionally measured lesions, persisting for 7 days, and occurring within 8 weeks of starting therapy. A relapse was defined the same as progressive disease but occurring after no change, an improvement, or partial or complete remission status; the minimal measurements obtained were used as the baseline for comparison. Remission duration was defined as the interval from the onset of response to relapse, whereas time to treatment failure was taken as the time from onset of treatment to relapse or progressive disease. Survival was measured from the beginning of therapy. Toxicity criteria are detailed in the text.

Kaplan-Meier (12) estimates of survival and time to treatment failure curves were obtained. A generalized Wilcoxon test and Mantel-Haenszel statistic were used to compare response curves (13). Additional statistical analyses were done using chi-squared and Fisher's exact tests for contingency table data and the Wilcoxon two-sample rank sum test (14). Regression techniques for exploring factors related to response were based on the logistic model for binary data (15). All *p*-values correspond to two-tailed tests and are significant if less than or equal to 0.05.

Results

PATIENT CHARACTERISTICS

A total of 121 patients were randomized between the two regimens; of the 108 patients considered evaluable, 52 received tamoxifen and 56 received tamoxifen and fluoxymesterone. Thirteen patients could not be evaluated because of inability to return to Bethesda for the initial and subsequent follow-up visit (3 patients), no measurable disease (3 patients), performance status less than or equal 30 (1 patient), major physician-related protocol violations within 10 days of starting protocol (2 patients), treatment with the wrong regimen (1 patient), and no data received (3 patients). Six of the 108 patients (2 on tamoxifen, 4 on tamoxifen and fluoxymesterone) were lost to follow-up before relapse; the data for these patients are censored at the time of last follow-up.

The two regimens were comparable with respect to the following pretreatment characteristics: institution entered from (85% of the patients from the National Cancer Institute); dominant site of involvement (51% visceral, 41% osseous, 8% soft tissue); number of organ sites of involvement (1 site, 24%; 2, 35%; 3 or more, 41%); age (under 40 years, 12%; 40 to 49 years, 24%, 50 to 59 years, 35%; 60 years or older, 29%); menopausal status (before, 6%; ablative postmenopausal, 40%; naturally postmenopausal, 54%); previous mastectomy (86%); number of previous chemotherapy regimens (none, 15%; 1, 53%; 2, 27%; 3, 6%) and response (first regimen, 64%; second regimen, 41%); number of previous hormonotherapy regimens (none, 40%; 1, 55%, 2, 6%) and response (46%); previous radiotherapy (66%); previous number of systemic therapy programs (none, 6%; 1, 33%; 2, 32%; three or more, 28%); median time from diagnosis to recurrence (tamoxifen, 16.5 months; tamoxifen and fluoxymesterone, 20.3 months); estrogen receptor status (positive, 42%; negative, 15%; equivocal, 6%; no data, 36%); performance status (90 or more, 45%; 75 to 89, 30%; under 75, 25%); analgesic requirements (none, 40%; non-narcotic, 19%; oral narcotics, 34%; parenteral narcotics, 7%); and twice daily dose of tamoxifen (under 12 mg/m^2 body surface area, 34%; 12 to 32, 42%; more than 32, 24%). Although not significant by either the Fisher's exact test or the Wilcoxon rank sum test, there was a slight imbalance with respect to premenopausal status (5 on tamoxifen and fluoxymesterone, and 1 on tamoxifen) and age over 50 (68% on tamoxifen and fluoxymesterone, and 60% on tamoxifen).

SIDE EFFECTS

The tamoxifen and fluoxymesterone regimen appeared to have a higher incidence of hepatic enzyme elevations (23% of patients versus 16%), edema (14% versus 4%), and masculinization (39% versus 0%); however, only the latter was significant ($p < 0.001$). Nausea with or without emesis was reported in 8% on tamoxifen and 12% on tamoxifen and fluoxymesterone. Major hematologic toxicities were similar with each regimen. Leukopenia below 4000/mm^3 was seen in 15% on tamoxifen and 25% on the combination regimen. Thrombocytopenia less than 100 000/mm^3 was seen in 10% on tamoxifen and 6% on the combination regimen. As previously described (10) these hematologic effects were transient and did not require dosage modifications. Hemoglobin decreases greater than 1 g/dL occurred in 25% on tamoxifen and 23% on the combination. Treatment-related hypercalcemia occurred in only one patient on each regimen. Approximately one patient in five on both regimens

Table 2. Times to Treatment Failure by Response Categories*

Response Category*	Tamoxifen		Tamoxifen and Fluoxymesterone		*p* Values	
	Patients	Median Time	Patients	Median Time	Log Rank	Wilcoxon Gehan
	n	*d*	*n*	*d*		
PD	26	36	14	21	0.029	0.001
NC	13	128	14(3)†	147	0.395	0.190
IMP	5(1)	84	7(1)	200	0.145	0.063
PR+CR	8(1)	286	21(4)	312	0.680	0.897
PD+NC+IMP	44(1)	56	35(4)	116	0.037	0.180
IMP+PR+CR	13(2)	203	28(5)	290	0.861	0.304

* PD = progressive disease; NC = no change; IMP = improvement; PR = partial remission; CR = complete remission.
† Number in parentheses is number of patients censored.

(19% and 20%) had an apparent "flare" as previously described (10). Reactions that were similar but indistinguishable from progressive disease occurred in an additional 2% on tamoxifen and 7% on tamoxifen and fluoxymesterone. The tamoxifen-related ocular toxicity from this trial was previously reported (16) and occurred only at higher doses in 2% on tamoxifen and 5% on the combination regimen. Additional side effects recorded in one patient each on tamoxifen were constipation, weakness, nocturnal leg cramps, superficial phlebitis, and vaginal spotting. On the tamoxifen and fluoxymesterone regimen the following additional side effects were reported in 14 patients: pancreatitis (1 patient), headaches (1 patient), decreased hearing with dizziness and ataxia (1 patient), blurred vision and weakness (1 patient), vaginal spotting (4 patients), hemoglobin increases (6 patients), increased areolar pigmentation (1 patient), insomnia (1 patient), depression (1 patient), and hot flashes (1 patient). Aside from the ocular toxicity, there was no indication that the side effects differed across tamoxifen dose levels.

Permanent dose modifications of fluoxymesterone were needed in seven patients due to rising liver function tests (four patients), nausea and vomiting (two patients), and acneiform lesions (one patient).

OVERALL THERAPEUTIC EFFECT

The response rate with tamoxifen and fluoxymesterone was superior to that with tamoxifen alone ($p = 0.0025$, Wilcoxon rank sum, Table 1). Complete remissions were seen only in the tamoxifen and fluoxymesterone group. The combined complete and partial remission rate was 15% with tamoxifen and 38% with tamoxifen and fluoxymesterone ($p = 0.016$, Fisher's exact test), and the combined complete and partial remission and improvement rate was, respectively, 25% and 50% ($p = 0.013$).

The median time from onset of a complete or partial remission to relapse (the remission duration) for the tamoxifen and fluoxymesterone group was 212 days (range, 44 to 1309 days) and for the tamoxifen group, 230 days (range, 77 to 953 days). The addition of patients classified as improved did not alter the tamoxifen and fluoxymesterone median; however, this addition reduced the tamoxifen median to 147 days. The differences between remission durations for the two treatment groups were not statistically significant.

The median time from onset of therapy to treatment failure was longer with the tamoxifen and fluoxymesterone regimen (180 versus 64 days, $p = 0.01$ Mantel-Haenszel test, $p = 0.006$ generalized Wilcoxon test; Figure 1). The median time to treatment failure for the separate response categories with each regimen are shown in Table 2. These results suggest that the major difference in time to treatment failure for the two regimens is due to the higher complete and partial remission rate and the longer time to treatment failure of the improvement patients on the tamoxifen and fluoxymesterone regimen.

The median survival of patients in the tamoxifen and fluoxymesterone group was 380 days (range, 19 to 1283 days; 42 of 56 patients died) and was longer than in the tamoxifen group (330 days; range, 16 to 974 days; 41 of 52 patients died). This difference was not statistically significant ($p = 0.17$, generalized Wilcoxon test).

RESPONSE BY STUDY CHARACTERISTICS

The remission rates seen for the study characteristics noted above tended to be higher with the tamoxifen and

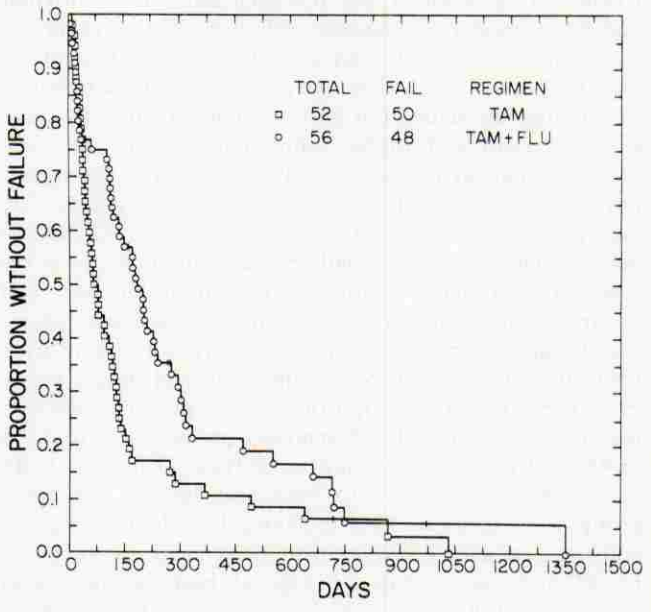

Figure 1. Comparison of time to treatment failure for all evaluable patients randomized to tamoxifen (*TAM*) and to tamoxifen and fluoxymesterone (*TAM + FLU*) ($p = 0.01$, Mantel-Haenszel; $p = 0.006$, generalized Wilcoxon).

Table 3. Effect of Tamoxifen Dose on Remission Rate

Regimen	Remission Category*	Effect of Tamoxifen Dose		
		< 12†	12-32†	> 32†
		← n(%)‡ →		
Tamoxifen	CR + PR	2/19(11)	2/21(10)	4/12(33)
	CR + PR + IMP	5/19(26)	4/21(19)	4/12(33)
Tamoxifen and fluoxymesterone	CR + PR	8/18(44)	6/24(25)	7/14(50)
	CR + PR + IMP	10/18(56)	10/24(42)	8/14(57)
Both regimens	CR + PR	10/37(27)	8/45(18)	11/26(42)
	CR + PR + IMP	15/37(41)	14/45(31)	12/26(46)

* CR = complete remission; PR = partial remission; IMP = improvement.
† mg/m^2 body surface area twice daily.
‡ Patients responding/total (%).

fluoxymesterone regimen. Patients receiving tamoxifen and fluoxymesterone also tended to have higher complete and partial remission rates in all evaluable sites, but this difference was significant only for soft tissue sites. Of interest was the trend toward more complete and partial remissions with the tamoxifen and fluoxymesterone regimen in patients who had not previously responded to hormone therapy (5 of 17 patients versus 1 of 11) or known to be estrogen-receptor-negative (2 of 9 versus 0 of 7). In addition there was a significant overall linear trend among the regimens favoring higher complete and partial remission rates for higher performance ratings, fewer numbers of previous hormone therapy or chemotherapy regimens, and a positive estrogen receptor status, as well as for complete and partial remission and improvement rates with disease-free intervals of 12 or more months.

DOSE-RESPONSE RELATIONSHIPS

The patients receiving tamoxifen alone tended to have a higher response rate with increasing tamoxifen dose (Table 3). This effect was not seen with the tamoxifen and fluoxymesterone regimen although the two regimens were comparable with respect to the combination of tamoxifen dose and other pretreatment characteristics. Combining the data from both regimens tended to abrogate the trend with higher tamoxifen doses in the complete and partial remission and improvement group but not in the complete and partial remission categories. The dose groupings of under 12, 12 to 32 and over 32 mg/m^2 body surface area twice daily were comparable with respect to regimen, institution, dominant disease, age group, menopausal status, estrogen receptor status, previous therapies, number of organ sites of involvement, time from diagnosis to recurrence, and analgesia status. However, there was a disproportion in the performance ratings ($p = 0.009$) with a Karnofsky index of less than 75 in 46% of patients receiving more than 32 mg/m^2 body surface area (compared to 19% and 20% in the other groups); 75 to 89 in 45% receiving less than 12 mg/m^2 body surface area (compared to 22% and 19% in the 12 to 32 and more than 32 mg/m^2 body surface area groups); and 90 or more in 58% receiving 12 to 32 mg/m^2 body surface area (compared to 35% at less than 12 and over 32 mg/m^2 body surface area).

The time to first response of a complete or partial remission was not different when all data from both regimens were combined (Figure 2). The median times are 41, 69 and 56 days, respectively, for groups receiving less than 12, 12 to 32 and more than 32 mg/m^2 body surface area twice daily. By including the improvement category, these respective median times change only to 32, 52 and 55 days. Similarly, a significant relationship was not shown between increasing tamoxifen dose and times to treatment failure (Table 4).

Discussion

The present trial was designed as a phase I evaluation of tamoxifen dosage and a limited phase III comparison of tamoxifen alone and with fluoxymesterone. As previously reported (10) the combination of tamoxifen and fluoxymesterone was better than tamoxifen alone with respect to remission rate and time to treatment failure. The actual remission durations were not different. Although not statistically different it is interesting that the improvement category for osseous disease appeared to be a less meaningful response category for tamoxifen alone than for the combination. When considered in the context of results with combination chemotherapy regimens (11) it appears that the improvement category may only reflect a true remission effect in regimens approaching or exceeding a 40% remission rate.

Among the pretreatment characteristics evaluated, the tamoxifen and fluoxymesterone combination tended to produce higher remission rates in all categories. Of particular interest was the higher remission rate irrespective of previous hormone effect, or estrogen receptor status among the tamoxifen and fluoxymesterone cohorts. It has been reported elsewhere that patients who did not respond to tamoxifen or fluoxymesterone may still respond to the alternate hormone; however, patients beginning therapy with tamoxifen and crossing over to fluoxymesterone survived longer than those on the reverse regimen (17). Because patients who did not respond to tamoxifen in the present trial were not crossed over to fluoxymesterone, a study comparing the combination to a sequential tamoxifen to fluoxymesterone approach would be useful. Although it is difficult to envision the sequential approach leading to a doubling of the overall time to treatment failure as seen with the combination in our trial, such a study would provide a needed follow-up trial in view of our results.

The superior rate of complete and partial remissions with the combination therapy compared with tamoxifen alone (38% versus 15%), and the observation that patients who did not respond to tamoxifen and fluoxymesterone may respond to the alternate drug (17), suggest that the drugs are cytocidal for different cellular cohorts in the tumor. Investigation of the mechanisms involved through further biochemical studies could provide the basis for more rational approaches to combined hormone therapy.

Although there is a suggestion that the remission rate to tamoxifen increases with dose, this trend does not hold in the presence of fluoxymesterone. Overall there is no clear advantage to using higher tamoxifen doses based upon either remission rate or time to treatment failure in our predominantly postmenopausal patients. It has been reported elsewhere that with lower tamoxifen doses 12 weeks of treatment are needed to achieve steady-state levels of tamoxifen and its major metabolites (18). If these measured levels of tamoxifen are relevant with respect to therapeutic effect, higher doses that would achieve those levels more rapidly (18) should lead to a shorter time to remission. Within the numerical constraints of this trial, the failure to find any support for this hypothesis suggests that either there is no dose-response effect in the range tested, or the parent compound and its major measured metabolites are not solely responsible for the antitumor effect. Although both explanations may in part be correct, the data in this study on remission rate, time to remission, and time to treatment failure support the overall lack of a clinically significant dose-response effect.

The side effects of tamoxifen and the addition of fluoxymesterone were similar to those previously reported (10). It should again be emphasized that the suppressed blood counts occurred in the first few weeks and did not require dose modification. The ocular toxicity previously reported from this trial (16) has not been seen at lower doses of 10 to 20 mg twice daily for up to 5 years in either our experience or that of others (19). A disturbing note continues to be the "flare" effect reported previously in greater detail (10). The severity of this reaction can make it difficult to evaluate whether the flare represents progressive disease or is the prodrome of a remission. Clearly the clinical severity and potential for life-threatening progression of these reactions over the first few weeks require considerable clinical judgment in deciding whether to continue tamoxifen treatment.

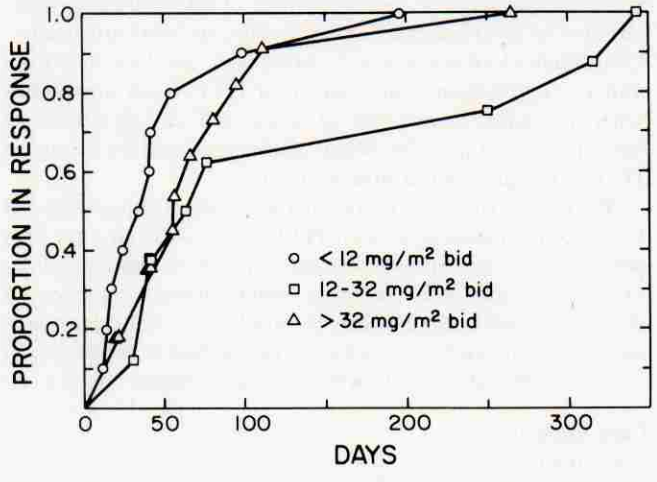

Figure 2. Relationship between tamoxifen dose (mg/m² body surface area twice daily) and time to at least a partial remission. All evaluable patients receiving tamoxifen alone and tamoxifen and fluoxymesterone are included. Bid = twice daily.

Table 4. Effect of Tamoxifen Dose on Time to Treatment Failure Percentiles

Tamoxifen Dose*	Patients	Time to Treatment Failure Percentiles		
		75th	50th	25th
	n	← *d(n)*† →		
< 12	37	39(24)	92(16)	227(6)
12-32	45	45(28)	128(17)	288(8)
> 32	26	29(20)	75(14)	235(7)

* mg/m² body surface area twice daily.
† Number of days (number of patients still at risk).

The overall results of the present trial suggest that there is not a meaningful dose-response relationship when the tamoxifen dose given twice daily ranges from 2 to 100 mg/m² body surface area and that the tamoxifen and fluoxymesterone regimen is therapeutically superior to tamoxifen alone in postmenopausal patients.

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The Human T-cell Leukemia/Lymphoma Virus, Lymphoma, Lytic Bone Lesions, and Hypercalcemia

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The human T-cell lymphoma (HTL) virus is a type C RNA tumor virus isolated from patients with malignancies of mature T cells. We report three patients with peripheral T-cell lymphoma, hypercalcemia, and antibodies to HTL virus. One patient presented with idiopathic hypercalcemia of 6 months' duration, two with striking lytic bone lesions, and two with circulating malignant lymphocytes. Malignant cells from all patients had surface markers characteristic of thymic-derived lymphocytes (T cells), and all patients had natural serum antibodies to disrupted HTL virus and to one or both viral structural proteins p19 and p24. Patients with adult peripheral T-cell lymphomas, particularly those that present with hypercalcemia and lytic bone lesions, may have antibodies to the type C RNA human tumor virus, HTL virus.

RETROVIRUSES have long been implicated in the induction of leukemia and lymphoma in a number of animals. The human T-cell leukemia/lymphoma (HTL) virus is the first type-C retrovirus consistently associated with human malignancy. Human T-cell leukemia virus was initially isolated from patients from the United States who had cutaneous T-cell lymphoma (1, 2) and is distinct from previously identified animal retroviruses as shown by hybridization studies of its nucleic acids (3), immunologic studies of its major core protein p24 (4), reverse transcriptase (5), and a second viral protein, p19 (6). Antibodies directed against proteins p24 and p19 have been identified in the sera of some lymphoma patients, and are markers of HTL-virus infection (7-11). Previous studies, showing that HTL-virus proviral sequences are present in the DNA of neoplastic T-cells (1), but not in DNA of non-neoplastic B cells from the same patient (12), show that HTL virus is an exogenous virus acquired by infection, and not transmitted in the germ line.

The first patient from whom HTL virus was isolated had a cutaneous lymphoma of mature T cells, classified clinically and pathologically as mycosis fungoides/d'emblee (1). Subsequent studies in the United States of over 200 patients with typical mycosis fungoides and Sézary syndrome show that association with HTL virus is unusual with this disease (Gallo RC, Kalyanaraman VS, Sarngadharan MG, et al. Association of the human type-C retrovirus, HTLV, with a subset of adult T-cell malignancies as evidenced by viral-specific natural antibodies. Unpublished observations). However, studies in Japan and the Caribbean that associated HTL-virus antibodies with a clinical syndrome of mature T-cell lymphomas have helped to identify other syndromes and locations of HTL-virus-associated disease (8-10).

We report three patients with a subset of mature T-cell lymphomas associated with HTL virus. All patients presented with advanced disease and were identified as HTL-virus antibody positive when stored samples of their sera were retrospectively analyzed. The virus was isolated from malignant cells of two patients when previously frozen tumor cells were placed in tissue culture.

Case Reports

PATIENT 1

A 45-year-old Israeli man, a food processing technician, developed anorexia, nausea, fatigue, peripheral edema, and mild renal failure in December 1980. Hypercalcemia (to 14 mg/dL) was discovered, and exploration of the neck failed to show para-

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