Clinical Pharmacology of Tamoxifen in Patients with Breast Cancer:

Correlation with Clinical Data

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Blood tamoxifen levels were determined for patients with metastatic breast cancer following initial and chronic dosing at twice daily 10 mg/m² or a 20 mg/m² single dose. Median time to response was six weeks. Blood tamoxifen levels at that time were ten-fold greater than those obtained after an initial single dose; however, steady-state values were not achieved until 16 weeks of chronic dosing. On a loading dose schedule of 40 mg/m² twice daily for seven days and 20 mg/m² daily thereafter, blood levels ≥ 10 mg/m² twice daily steady-state values were reached in one week. Levels drawn at peak and trough times suggest that tamoxifen may be given on a once-daily basis. Tamoxifen half-life was 9–12 hours after the initial dose and seven days after chronic dosing.

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TAMOXIFEN is an antiestrogen currently being used in the treatment of breast cancer, particularly in the postmenopausal patient. The response rate of 37% achieved in postmenopausal women[3,16,18,20,21,27,29] compares favorably with that of androgens (22%),[4,5,11] estrogens (26%),[2,5] adrenalectomy (30%),[6,7,24] and hypophysectomy (30%).[8,17,22] Its comparative effectiveness with oophorectomy with premenopausal patients has yet to be fully delineated. A total of 70 such cases have been reported with a cumulative response rate of 27%.[1,12,16,18,20,23,29] Although this compares favorably with the 30% response rate reported for oophorectomy,[7,26,28] a sizable proportion of patients were having some menopausal symptoms when tamoxifen therapy was begun. Side-effects appear to occur less frequently with tamoxifen than with the other common forms of treatment.[14,16,18,20,27]

Despite its current popularity, surprisingly little is known about the pharmacokinetics of tamoxifen because of difficulties in developing a specific assay using a nonradiolabeled drug. Fromson *et al.*[10] studied reactions of a variety of animals (rats, mouse, dog, and monkey) to carbon-14-labeled tamoxifen. Maximum serum levels appeared 1 to 6 hours after administration with a prolonged half-life of greater than 24 hours. In rats and dogs, tamoxifen and its metabolites were conjugated and excreted into the bile. The majority of this pool was then reabsorbed after hydrolysis of the conjugates in the gut. The remainder was excreted in the feces. Urinary excretion was determined to be unimportant. Owing to the enterohepatic circulation, excretion was prolonged. A period of ten to 20 days was needed in order to eliminate 90% of the radioactivity from a single dose.

Fromson[9] also studied four female patients receiving tamoxifen, again using the carbon-14 method.[9] Feces and urine from two patients were collected. After a single dose equivalent to 12 mg/m², maximum levels of tamoxifen were reached 4–7 hours after administration. An initial half-life of 7–14 hours was noted with a secondary half-life of more than seven days. Again, there was prolonged fecal excretion over several weeks.

Due to the long half-life of tamoxifen (demonstrated with the carbon-14 label) we thought it possible that blood tamoxifen levels after initial administration might be quite different than those after chronic dosing and that this might having bearing on the length of time needed to achieve a therapeutic response. We were also interested in determining the half-life after chronic dosing. Kinetic data after chronic dosing might be

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potentially useful in determining the appropriate interval between discontinuation of tamoxifen therapy and biopsy sampling for estrogen receptor without running a substantial risk of obtaining a false-negative result. Using a specific analytic method for (non-radiolabeled) tamoxifen,[19] we investigated these possibilities.

Materials and Methods

The study consisted of two phases. In Phase I, blood tamoxifen levels for 25 patients with metastatic breast cancer were determined after the initial dose and during and after treatment at a commonly used dose schedule of 10 mg/m² twice daily (to the nearest 10 mg). In Phase II, similar pilot data were gathered regarding three loading dose schedules and a single daily dose schedule.

A total of 37 patients with metastatic breast cancer participated in the study. Median performance status was 1 (symptomatic but ambulatory and capable of normal work activities). Eleven patients had had no prior systemic therapy. The remaining patients had had prior hormone therapy or chemotherapy or both. The median patient age was 57 years. Three patients were premenopausal and 34 patients were postmenopausal.

Before entering the study, each patient was evaluated with x-rays of the chest, skull, spine, ribs, and pelvis, liver scan, complete blood count with differential, calcium, phosphorus, SGOT, SGPT, alkaline phosphatase, bilirubin, BUN, creatinine, and blood estradiol levels. Estrogen receptor determinations were performed before treatment when possible with the dextran-coated charcoal technique. Specimens containing less than 3 fentomoles of receptor per milligram of cytosol protein were considered negative, 3–9 borderline, and those containing more than 10 fentomoles were considered positive. Complete blood counts and platelet counts were redone ten days after treatment was begun and every four to eight weeks thereafter, along with renal and liver function studies. Clinical follow-up examinations and x-rays of involved sites were performed at four to eight week intervals.

In Phase I of the study, blood samples for determination of blood tamoxifen levels were drawn at 0, ½, 3, 6, 9, and 12 hours after the initial dose, and then at 3 and 12 hours post dose on a monthly basis. For two patients receiving 10 mg/m² twice daily, blood tamoxifen levels were measured at weekly intervals for six weeks after tamoxifen was begun; in addition to blood samples taken at 3, 12, 24, and 48 hours after the first dose. After the initial six weeks, samples were obtained at 3 and 12 hours post dose every four to eight weeks. Blood samples were collected in heparinized glass tubes and samples were frozen until analysis was performed.The methodology for determining blood tamoxifen levels was developed by Mendenhall *et al.*,[19] using direct extraction, photochemical activation, and chromatographic analysis as previously reported.[19] This methodology discriminates between the parent drug and the metabolite. Blood tamoxifen levels (parent drug) were reported in nanograms per milliliter of whole blood. Intraassay variability is ±3% and interassay variability, ±5%.

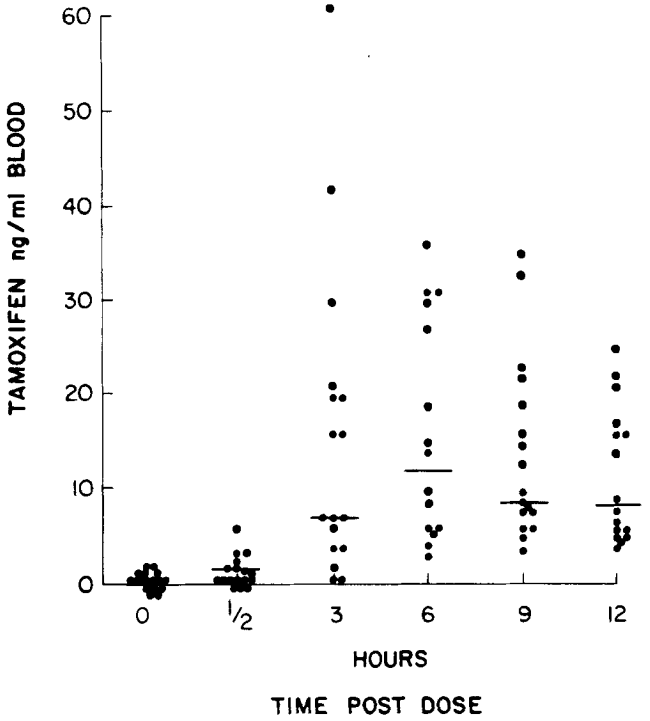

FIG. 1. Blood tamoxifen levels following a single dose of 10 mg/m² in 17 patients.

The purpose of Phase II was to gain some preliminary information regarding blood tamoxifen levels on a single daily dose schedule as well as on several loading dose schedules. For two patients receiving single daily doses of 20 mg/m², blood tamoxifen levels were measured at 3, 12, 24, and 48 hours after the initial dose, at weekly intervals for six weeks, and then at 3 and 24 hours post dose every four to eight weeks thereafter.

Four patients each received a loading dose of 20 mg/m² twice daily for seven days and a 20 mg/m² single daily dose thereafter. Four patients each received a loading dose of 40 mg/m² twice daily for seven days and a 20 mg/m² single daily dose thereafter. Two patients each received a loading dose of 80 mg/m² twice daily for seven days and a 20 mg/m² single daily dose changed thereafter. All doses on the loading dose schedule were to the nearest 10 mg. Time of blood

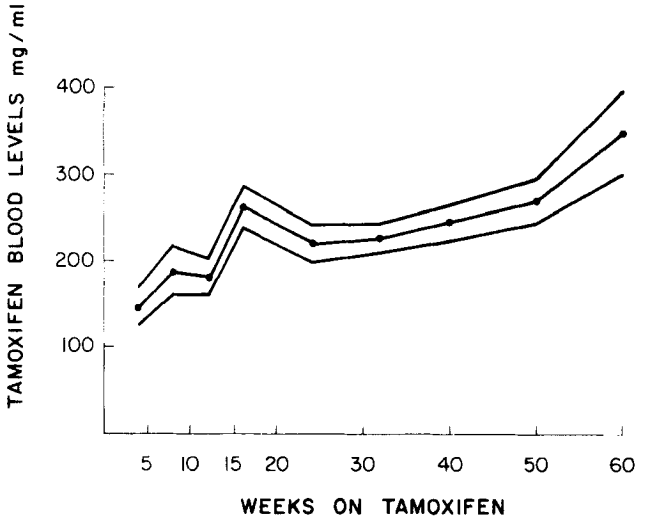

FIG. 2. Mean blood tamoxifen levels ± 1 S.D. in 12 patients at a dose of 10 mg/m² twice daily using both the 3-hour and 12-hour post-dose values.

sampling varied slightly for patients on the loading dose schedule, but at minimum, samples were drawn at 3 and 12 hours post dose on days 1, 4, (96 hours), and 7, and then at 3 and 24 hours post dose weekly for eight weeks. After the first eight weeks on study, blood samples were drawn at 3 and 24 hours post dose every two months.

In both phases of the study, blood samples were also obtained after treatment had failed and tamoxifen therapy was terminated. The first sample was always drawn 3 hours after the last dose was given. Samples were then drawn at 24, 48, and 72 hours and weekly for six weeks after the last dose.

Criteria for response were those recommended by the Breast Cancer Task Force.[13] An improvement category was also added, defined as a less than 50% but greater than 25% decrease in the sum of the products of the diameters of measured lesions. The response duration was defined as the time from onset of response to relapse or increasing disease. For analysis pertaining to two groups, a one sided t-test was used. For analysis pertaining to three groups, a one way analysis of variance was used.

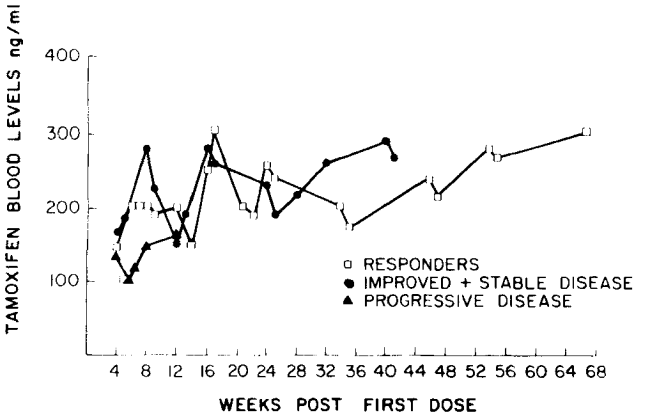

FIG. 3. Comparison of blood tamoxifen levels in responding and nonresponding patients at a dose of 10 mg/m² twice daily using both the 3-hour and 12-hour post-dose values.

Results

Blood Tamoxifen Levels: Phase I

Twenty-three patients each received a dose of 10 mg/m² twice daily and blood tamoxifen levels were determined at 0, ½, 3, 6, 9, and 12 hours after the initial dose and every four weeks thereafter.

Single-dose kinetic data (Fig. 1) were available for 17 patients in Phase I. The median peak level after a single dose was reached in a median time of 6 hours. The median half-life was greater than 6 hours and could not accurately be determined. For four additional patients (two at 10 mg/M² twice-daily BID and two at 20 mg/m² single dose), blood samples were drawn at ½, 3, 12, 24, and 48 hours after the first dose. The half-life appeared to be between 9 and 12 hours (after peak levels were reached).

Twelve patients received tamoxifen for prolonged periods of time. Figure 2 gives mean tamoxifen values ±1 SD after chronic dosing, utilizing both the 3-hour and 6-hour post-dose values. After four weeks, the mean blood tamoxifen level was 144 which was ten times higher than that obtained after a single dose. Mean steady-state values were not obtained, however, until patients had received drug for 16 weeks. The median time to response was six weeks. The lowest tamoxifen level at this time in a responder was 70 ng/ml. The lowest steady-state value in a responder was 150 ng/ml.

Nineteen patients received drug for four or more weeks and were thought to have consistently taken their tamoxifen. In this group, 58 sets of 3-hour post-dose and 12-hour post-dose blood samples were drawn on the same day. Values at 3 hours post dose (median, 206 ng/ml) were not different from those measured at 12 hours post dose (median, 182 ng/ml). Levels at 3 and 12 hours in responders were not significantly different from those in nonresponders (Fig. 3).

Blood Tamoxifen Levels: Phase II

Blood tamoxifen levels after four weeks and steady-state values were at least 1 log higher than those obtained after a single dose, but it was unknown how quickly the steady-state values were being reached. Also, since there was no difference between values obtained at 3 hours and those obtained at 12 hours on

chronic dosing, it was possible that a single daily dosage would be adequate.

In order to clarify these points, we studied four patients receiving 10 mg/m² twice daily or 20 mg/m² once daily with interval samplings between 12 hours and four weeks on study. The median steady-state value for this group was 333 ng/ml. Steady-state values were not achieved until four weeks had passed and then in only three or four patients. Average values after one, two, three, and four weeks were 107, 156, 158, and 375 ng/ml, respectively. Values were below 150 ng/ml in two of four patients after one and two weeks, in one of two patients after three weeks, and in one of four patients after four weeks (Fig. 4).

In an effort to quickly achieve a steady state as well as a level of tamoxifen which was known to be therapeutic, ten patients were given loading doses of tamoxifen for seven days. Four patients received 20 mg/m² twice daily; four patients, 40 mg/m² twice daily; and two patients, 80 mg/m² twice daily. After the initial seven days, each patient was given a single daily dose of 20 mg/m². At 20 mg/m² twice daily, three of four patients reached the median steady-state value for the group (241 ng/ml) within a week (Fig. 5). At the 40 mg/m² BID level, all four patients reached the median steady-state value for the group (328 ng/ml) within a week, and all were within the range known to be associated with response in our patients (>150 ng/ml) by 72 hours as all had blood tamoxifen levels of at least 225 ng/ml (Fig. 6). In two cases, increasing the initial dose to 80 mg/m² twice daily for seven days resulted in blood tamoxifen levels of 225 ± 15 ng/ml (levels known to be associated with response) within 3 hours following the initial dose.

In order to determine whether adequate blood tamoxifen levels could be sustained if tamoxifen were given once daily, two patients were given 20 mg/m² orally once a day. Ten patients were given 20 mg/m² orally once daily after being given initial seven day loading doses of 20–80 mg/m² (as described earlier). Blood tamoxifen levels were determined at 3 and 24 hours post dose weekly for the first six to eight weeks and then every four to eight weeks thereafter. Median blood tamoxifen levels after chronic dosing (at least 4 weeks on study) at the 20 mg/m² single daily dose level were 376 ng/ml at 3 hours and 262 ng/ml at 24 hours post dose. The analysis was done on 14 sets of 3-hour and 24-hour samples drawn in the same day. Although there was a greater spread in these values than with twice daily dosing, the 24-hour value was still well above a level shown to be associated with response.

Serial blood levels were determined for 17 patients after discontinuation of tamoxifen (Fig. 7). The median half-life was seven days (range, three to 21 days). The

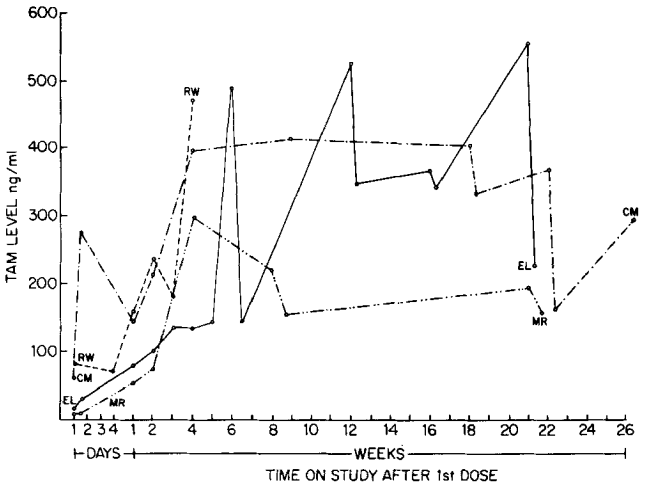

FIG. 4. Blood tamoxifen levels in patients receiving 10 mg/m² twice daily or 20 mg/m² single daily dose.

median time to reach blood tamoxifen levels of less than 70 ng/ml (known to be associated with response) was 21–28 days. Tamoxifen was still detectable six weeks after treatment was stopped.

Clinical Data

Response Data

Thirty-three patients were considered fully evaluable for response. Two patients did not have measurable disease and were thus not considered evaluable. One patient died after eight days on study, probably of a pulmonary embolism, and one patient had a flare reaction and refused further treatment after two weeks on study. These two patients were considered partially evaluable. The overall response rate for fully and

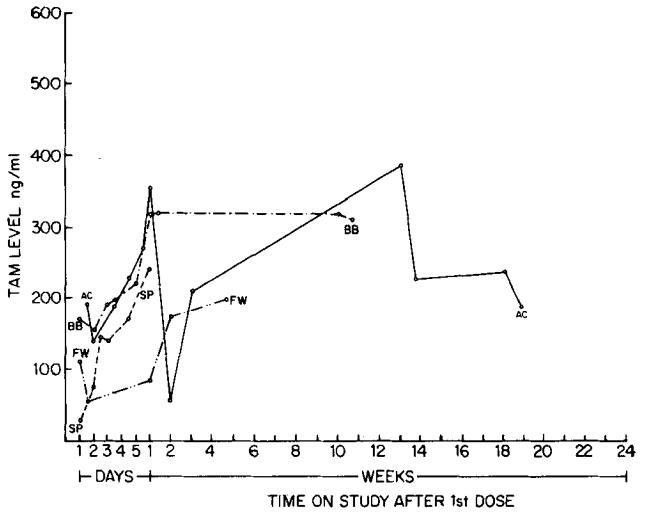

FIG. 5. Blood tamoxifen levels in patients receiving 20 mg/m² twice daily for seven days and 20 mg/m² single daily doses thereafter.

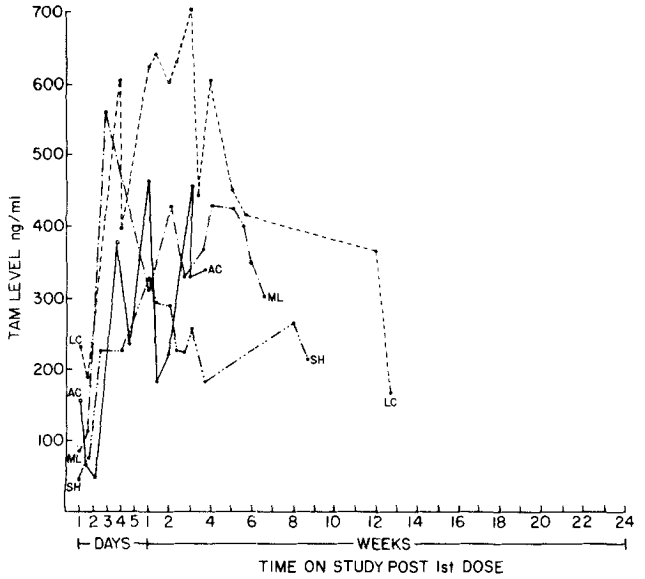

FIG. 6. Blood tamoxifen levels in patients receiving 40 mg/m² twice daily for seven days and 20 mg/m² single daily doses thereafter.

partially evaluable patients was eight of 35 (23%). The median time to response was six weeks and the median duration of response was 36 weeks. Patients with stable disease had a median time of 24 weeks to disease progression. Of the 24 fully or partially evaluable patients receiving 10 mg/m² twice daily seven (29%) responded. No response was seen for the nine fully evaluable loading dose patients; Of these, however, 67% had bone metastases as their evaluable lesions which are traditionally difficult to evaluate. It is of note that four of the nine had improvement or prolonged stable disease lasting from 22 to 75+ weeks.

Increasing disease was observed in the three premenopausal patients (two received doses of 10 mg/m² twice daily and one, the 40 mg/m² twice daily loading dose schedule.) Estrogen receptor status was

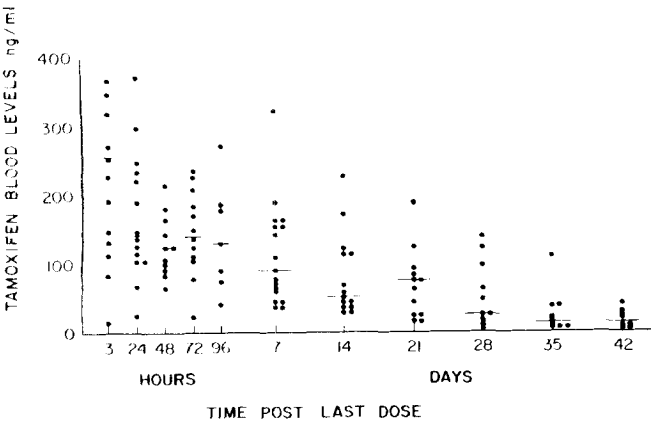

FIG. 7. Blood tamoxifen levels after discontinuation of tamoxifen past chronic dosing at 10 mg/m² twice daily in 17 patients.

borderline for one and unknown for two; levels varied from 26 to 88 pg/ml (normal premenopausal range, > 26 pg/ml). Response rates for postmenopausal women receiving 10 mg/m² twice daily was 32%.

Pretreatment estradiol levels were determined for 23 of the response-evaluable patients receiving doses of 10 mg/m² twice daily. Five patients had estradiol levels of more than 26 pg/ml (premenopause range). Clinically, three of these patients were postmenopausal and two were premenopausal. No response was observed in the group of patients with estradiol levels of more than 26 pg/ml.

Estrogen receptor determinations were performed for 11 patients who were response evaluable. Six patients were estrogen-receptor positive. In this group, one patient had a partial response; one, improvement; two, stable disease; and two, increasing disease. Seven additional patients did not have estrogen receptor determinations but had had prior hormone response. In this group, two patients had complete responses; two, partial responses; two, stable disease; and one increasing disease. No response was observed for the five patients who were negative or borderline for estrogen receptor determination. Of 16 response-evaluable patients who neither had estrogen receptor determination nor a previous hormone trial, three responded.

Of three patients who had previously undergone adrenalectomy, two had responded to the ablative procedure. All three responded to tamoxifen. Response may have resulted from competitive inhibition with estrogens at the receptor site, since maintenance hydrocortisone is partially converted to 11-8-OH-estradiol in oophoadrenalectomized individuals.[25]

Toxicity

Of the 37 patients, 13 experienced toxic reactions (Table 1). The patient who exhibited probable paroxysmal atrial tachycardia was receiving a loading dose of 80 mg/m² twice daily. She had no later difficulties when the drug was withdrawn for two days and she was started on the 20 mg/m² single daily dosage. One patient had incapacitating headaches at 20 mg/m² (40 mg) per day. She tolerated the drug well at 10 mg/m² per day. Both patients with flare reactions had predominant metastatic bone lesions. The flare consisted of a marked increase in bone pain in involved areas, seen within a few days of starting tamoxifen and lasting up to two weeks. One patient was positive for estrogen receptor and went on to achieve a partial response lasting 36 weeks. In the other patient, estrogen receptor determination was not done and the patient refused further therapy after two weeks.

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