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Tamoxifen (Nolvadex*) Therapy – Radionale for Loading Dose Followed by Maintenance Dose for Patients with Metastatic Breast Cancer

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Summary. *A loading dose of tamoxifen 100 mg/m² on day 1, followed by a maintenance dose of 20 mg daily, achieved mean* parent *drug concentrations of greater than 150 ng/ml in 12 of 12 patients with metastatic breast cancer. This drug concentration was achieved on day 1 and maintained throughout the study period (28 days). This rapid achievement of steady-state serum concentrations may be of therapeutic benefit in the management of patients with tamoxifen-sensitive tumours.*

Introduction

The anti-oestrogenic drug tamoxifen (T) is now used extensively in the management of metastatic breast cancer. The conventional method of administration is to give 20–40 mg daily in divided doses, which in the majority of sensitive patients does not give a clinical response in less than 6 weeks. We have previously demonstrated that with a dose of 10 mg b.d., steady-state serum concentrations were not achieved in 3 weeks and that this observation may be relevant to the delay in initiation of response [10]. It was suggested that a loading dose followed by a maintenance dose could overcome this delay in reaching steady state and might induce more rapid clinical response. We now report a pilot study to test this hypothesis.

Patients, Materials and Methods

Patients. Fifteen patients with metastatic breast cancer were selected for treatment after the study had been explained in detail and informed consent obtained. Patients' liver function was considered to be normal where the liver was not palpable clinically and where serum albumin, bilirubin, and liver enzymes were within normal limits. All patients treated fulfilled these criteria; it was not considered appropriate to undertake more detailed assessment of hepatic function. Similarly, renal function was considered to be normal in each patient in whom the serum creatinine was within the normal range for the patient's age, and all patients had normal renal function according to this criterion.

Three loading dose regimens were selected and administered to three separate patients in a pilot study. The loading dose for regimens 1, 2, and 3 was fractionated over 24 h in multiples of 40 mg. Thus 160 mg was administered as four 10-mg tablets 4-hourly × 4.

Regimen 1
100 mg day 1; 80 mg day 2; 60 mg days 3, 4; 40 mg days 5, 6, 7; and 20 mg daily thereafter.

Regimen 2
160 mg day 1; 20 mg daily thereafter.

Regimen 3
100 mg day 1, 20 mg daily thereafter.

Blood samples, obtained on days 0, 1, 2, 7, 14, and 28, were collected in plain tubes and allowed to clot at room temperature. Serum was obtained by centrifugation and stored at −20° C prior to assay. Further samples were obtained on day 76 (regimen 1) and on day 47 (regimen 3). T and *N*-desmethyltamoxifen (DMT) concentrations were determined by the method of Adam et al. [2, 3].

In terms of simplicity and practicality in achieving the desired objective, regimen 2 appeared the most appropriate and therefore a further 12 patients were studied in the above manner.

Results

Figure 1 illustrates the serum concentrations of T and DMT on the three regimens in the pilot study.

Regimen 1

A peak T concentration of 300 ng/ml was achieved by day 2, followed by a gradual decline to 172 ng/ml at day 28. The peak concentration of DMT was not reached until day 14 and thereafter exceeded that of parent drug. Taking the day 76 result as final steady state in this patient, it can be seen that with this regimen the T values were always in excess of the final steady state but that the metabolite levels took 14 days to achieve/exceed the final value.

Regimen 2

Serum concentrations of T remained fairly constant from days 1 to 28, with the exception of a small fall on day 2. Peak concentrations of DMT were achieved by day 14 and were in excess of those of the parent drug.

Regimen 3

If the day 47 result was taken as final steady state in this patient the T concentration only achieved this value by day 28 and the metabolite levels did not achieve steady state by day 28.

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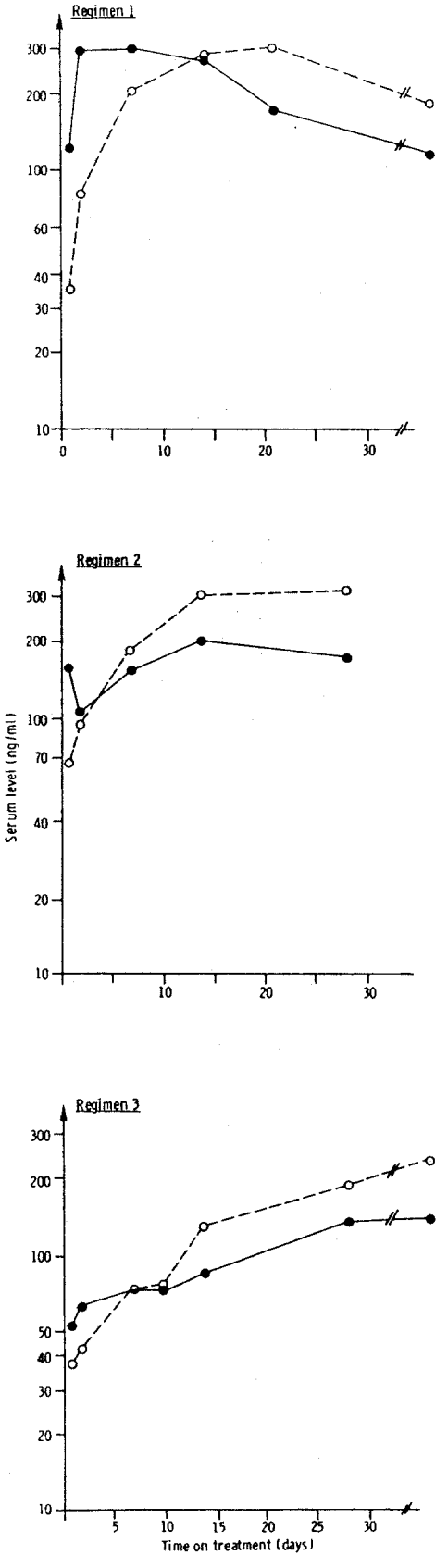

Fig. 1. Serum concentrations of tamoxifen (●) and *N*-desmethyltamoxifen (○) achieved by three loading dose regimens: 1, 100 mg on day 1, 80 mg on day 2, 60 mg on days 3 and 4, 40 mg on days 5, 6, and 7, and 20 mg daily thereafter; 2, 160 mg on day 1 and 20 mg daily thereafter; and 3, 100 mg on day 1 and 20 mg daily thereafter

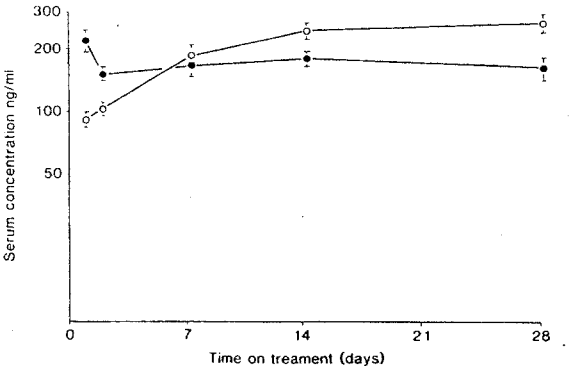

Fig. 2. Mean serum concentrations (mean ± SEM) of tamoxifen (●) and *N*-desmethyltamoxifen (○) in 12 patients treated with a loading dose of 160 mg followed by a maintenance dose of 20 mg daily

The mean concentrations of T and DMT achieved in the additional 12 patients studied on regimen 2 are shown in Fig. 2. Steady-state concentrations of T were achieved by day 2; the concentration of DMT gradually increased to achieve a steady state on day 14 and thereafter remained in excess of the parent drug concentration. No adverse effects were noted in any of the patients treated.

Discussion

The concept of a loading dose followed by a maintenance dose is a principle commonly applied to a situation where it is necessary to achieve an effective therapeutic concentration rapidly. What bedevils cancer therapy is the lack of information concerning what is an effective concentration of the therapeutic agent.

Tamoxifen is no exception, in that attempts to correlate serum concentrations with effect have failed to show a clear relationship between these parameters. One group failed to find any relationship [7], while another has stated that a concentration of greater than 150 ng/ml is consistent with response [4], although in the original study by these workers it was shown that levels in responders were not significantly different from those in non-responders [5].

With conventional T therapy, steady-state concentration for parent drug and metabolite were not achieved until after 4 and 8 weeks, respectively [2], whilst other workers have claimed that periods of up to 16 weeks are required to achieve a steady state [5]. Time to clinical response is generally accepted as being at least 6 weeks, and median values of 5, 3, 6, or 9 weeks have been reported [6–8]. Thus a loading dose regimen with T that would allow concentrations of parent drug in excess of 150 ng/ml to be reached within 48 h of commencing therapy could be a useful approach.

No information is available concerning relevant concentrations of DMT, but it should be recognised that this metabolite may contribute to the therapeutic effect in man as there is evidence of anti-oestrogenic activity in animals equal to that of parent drug [9].

Conceptually it can be argued that a loading dose should be more beneficial providing it is free from toxic effects and patient compliance is satisfactory. Although regimen 1 achieved the highest initial serum concentration it is probably too complicated for satisfactory patient compliance. Regimen 3 failed to yield adequate serum concentrations. With regimen 2, i.e., a loading dose of 100 mg/m^2 on day 1 followed

by a maintenance dose of 20 mg daily, peak concentrations of T greater than 150 ng/ml were achieved in all patients by day 1, and this was maintained throughout the study period. Concentrations of DMT achieved a steady-state level by day 14 and were in excess of those of T for the remainder of the study period. It would be more difficult to devise a regimen that could achieve steady-state concentrations of DMT quickly, as factors governing the metabolism of drugs are complex and the dose regimen selected would almost certainly have to be varied because of the heterogeneous nature of patient groups.

The results in this study can be contrasted with those of Fabian et al. [10], who observed that a loading dose of 40 mg/m^2 b.i.d. daily for 7 days yielded serum concentrations > 200 mg/ml within 3 days. Concentrations considerably in excess of these were attained from day 4 onwards even with a maintenance dose of 20 mg/m^2 daily. On present evidence of T kinetics a b.d. loading schedule over 7 days is somewhat excessive and daily administration would probably be sufficient. The selection of the loading dose in this study was derived from our previous study. For practical purposes it was felt that the most simplistic regimen suitable for patient compliance should be selected and we suggest that regimen 2, with approximately 100 mg/m^2 on day 1, is adequate to achieve serum concentrations currently believed to be satisfactory, and that this schedule could be used in the context of a clinical trial.

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