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Letter to the editors

Elevated plasma tamoxifen levels in a patient with liver obstruction

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Sirs,

Tamoxifen is an antiestrogen currently used in chemoendocrine therapy for advanced breast cancer [3, 6]. One form of chemoendocrine therapy, estrogen priming, uses tamoxifen in combination with estrogens for synchronizing tumor cell cycles [1, 2, 8]. The goal of estrogen priming is to enhance the cytotoxic effects of cancer chemotherapy by modulating tumor cytokinetics; the rationale is to stimulate cell division with estrogens and inhibit cell growth with antiestrogens. During the period of increased cell growth, cancer chemotherapy (CMF) is carried out with the goal of enhancing its cytotoxic properties, while antiestrogen therapy is used to inhibit tumor progression [1, 2, 5, 7, 8]. The pharmacologic modulation of estrogen- to antiestrogen-ratios may lead to improved treatment of patients with breast cancer. In the case presented, we report elevated tamoxifen and active tamoxifen metabolites in a woman with liver obstruction. In this situation, a potential drug-drug interaction may occur with tamoxifen and cell-cycle-specific chemotherapy, resulting in antiestrogen-to-estrogen ratios that would favor cell-cycle inhibition.

Patient history: A 36-year-old woman had a right modified radical mastectomy for a 1.5-cm, poorly differentiated, infiltrating adenocarcinoma of the breast in 1984. Estrogen receptors were weakly positive (21 fmol/mg); metastatic evaluation was negative. In March 1987 the patient was diagnosed as having a metastatic adenocarcinoma of the liver. Her liver function tests showed the following-bilirubin, 1.1 mg/dl (normal limits 0.1–1.2); alkaline phosphatase, 531 IU/l (normal limits 41–133), aspartate aminotransferase (AST), 293 IU/l (normal limits 7–39); and lactic dehydrogenase (LDH), 548 IU/l (normal limits 88–230). No other metastatic disease was identified, and the patient underwent chemoembolization of the liver with gelfoam, mitomycin C, adriamycin, and cisplatin. She was also started on a regimen of 20 mg tamoxifen citrate twice daily. The patient became jaundiced 4 months after chemoembolization, with grossly evident ascites and liver enlargement. Her liver function tests showed a bilirubin level of 4.7 mg/dl, an alkaline phosphatase level of 628 IU/l , an AST level of 155 IU/l, and an LDH level of 1175 IU/l. A CAT scan showed an increase in the size and number of liver lesions. The patient then received cyclophosphamide, methotrexate, and 5-fluorouracil; the tamoxifen was discontinued. Levels of plasma tamoxifen and its active metabolites were determined 2, 22 and 29 days after the final dose and are reported in Fig. 1 [9].

Darbe et al. have shown that estrogens have a higher receptor-binding affinity than the antiestrogen tamoxifen (1000:1) [4]. When antiestrogen-to-estrogen ratios are $<1000:1$, cell growth is stimulated, whereas ratios $>1000:1$ cause growth inhibition. We have recently shown that the ratio of plasma tamoxifen- and desmethyltamoxifen-to-plasma estrogen concentrations necessary for this cytokinetic modulation can be clinically obtained [2]. The average active tamoxifen and desmethyltamoxifen steady-state concentrations are approximately 200 and 300 ng/ml, respectively, on a regimen of 20 mg b.i.d. These concentrations typically exceed the necessary antiestrogen-to-estrogen ratios for growth inhibition and are approximately one-third of those seen in our patient (see Fig. 1).

Delayed elimination of tamoxifen and its active metabolites may occur in patients with liver metastases since the elimination of these compounds occurs primarily through liver metabolism and biliary excretion. Thus, the steady-state plasma antiestrogenic concentrations determined in our patient at the time of CMF therapy may have far ex-

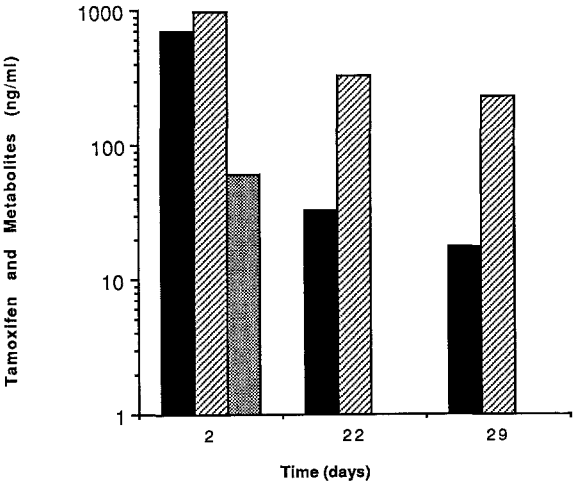

Fig. 1. Plasma tamoxifen (*solid*), desmethyltamoxifen (*dashed*), and 4-hydroxytamoxifen (*dotted*) levels after 4 months of tamoxifen at 20 mg b.i.d. Time 0 represents the final tamoxifen dose

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ceeded those necessary to achieve growth inhibition. Under these conditions, the maximal benefit from CMF therapy may not be realized. Thus, dosing modifications of tamoxifen therapy may be necessary to acheive the desired cytokinetic modulation in a patient with delayed elimination processes. Further research addressing this potential drug-drug interaction is warranted.

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