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Clinical Effects on CA 15-3 Level of Cyclosporin A as a Chemosensitiser in Chemoresistant Metastatic Breast Cancer

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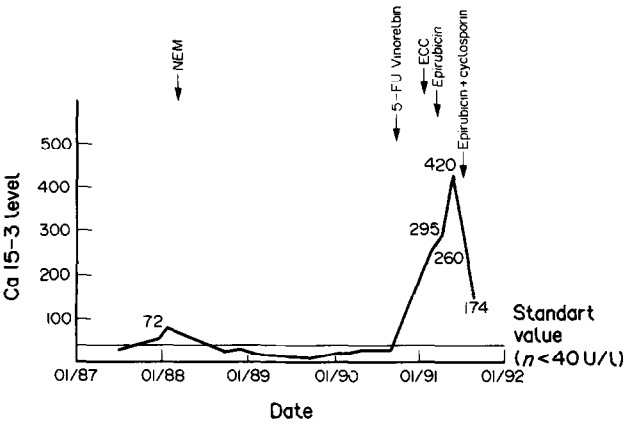

Fig. 1. Time evolution of Ca 15-3 values observed during the patient's follow-up.

THE SELECTION of drug-resistant cell lines is one of the major factors interfering with the clinical effectiveness of cytotoxic drugs. The P-glycoprotein (P-gp), an energy-dependent drug efflux pump, associated multidrug resistance phenotype (mdr 1) is the most extensively studied model [1–3]. In recent years, attempts have been made to circumvent P-gp by the use of additional compounds which either compete with or block P-gp. Cyclosporin A is an effective inhibitor of drugs efflux in mdr-positive cells *in vitro* [4]. We report here an observation of the clinical efficacy of the association of cyclosporin A with high-dose epirubicin after failure of high-dose epirubicin alone.

The patient, a 58-year-old woman, presented in October 1985 with a right breast adenocarcinoma (T3 N1b M0). She received six courses of polychemotherapy with doxorubicin, resulting in a 80% decrease in the clinical size of the breast tumour and the disappearance of the axillary node. Radiation therapy led to the complete regression of the tumour and was followed by four additional courses of the same chemotherapy. In 1988, a systematic check-up revealed a significant increase of Ca 15-3 level related to an isolated bone metastasis of the left iliac wing. The patient was treated by a second line chemotherapy, including vindesine and mitoxantrone. Following the sixth course, the Ca 15-3 was normal and a repeat bone scan showed a significant reduction of abnormal fixation. In May 1990, Ca 15-3 increased again and the patient complained of a painful neck because of bone metastasis at the C6 level. There was no improvement with vinorelbin or with cisplatin-cyclophophamide-VP 16 combination. In June 1991, a course of high-dose epirubicin (150 mg/m^2 D1) failed to bring relief of pain and Ca 15-3 continued to increase. The patient was given high-dose cyclosporin A (5 mg/kg) in a 6-h infusion in order to saturate the presumed tumour cell P-gp sites. Epirubicin (150 mg/m^2) was given intravenously in a short 15-min infusion 2 h after the cyclosporin A infusion began. The total blood concentrations of cyclosporin A, 2 and 6 h after beginning the infusion, were 177 and 3700 ng/ml, respectively. No side-effects were observed during treatment. On day 8, the patient developed a WHO grade III neutropenia without infection and white blood cell recovery occurred 5 days later. 3 weeks following the administration of epirubicin-cyclosporin A, the patient experienced complete relief pain and the Ca 15-3 levels decreased by 2.5-fold in duplicate blood sample (Fig. 1). Despite this encouraging result, she refused further chemotherapy as she was satisfied with the results obtained.

This case-report seems to demonstrate the clinical efficacy of the epirubicin-cyclosporin A combination in a breast cancer patient who initially responded to anthracyclins and plant alkaloids and developed a probable multidrug resistance at the time of the second relapse. Unfortunately, we failed to correlate this clinical result with the expression of P-gp and mdr1 mRNA in tumour cells because of the impossibility of harvesting tumour cells. However, only a few clinical studies of the reversal of mdr have been published [5, 6] and to our knowledge, there is no clinical report of the use of cyclosporin A to treat a mdr solid tumour. Since this epirubicin–cyclosporin A regimen proved to be feasible and well-tolerated on an out-patient basis, we feel that it may be worthwhile testing it in a larger pilot study.

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