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Phase II Study of Liposome-complexed Mitoxantrone in Patients With Advanced Breast Cancer

B.C. Pestalozzi, A. Vass, H. Adam, D.H. Horber, R.A. Schwendener and Chr. Sauter

LIPOSOMAL PREPARATIONS may have advantages over free drugs, for example, selective localisation in tumours through fenestrated capillaries, and prolonged drug exposure through increased half-life. We have incorporated mitoxantrone into liposomes by combining it with phosphatidic acid [1], and in a human phase I study defined a recommended dose of 18 mg/m^2 of liposome-complexed mitoxantrone (LCM) [2]. Based on a randomised study, we chose to treat our advanced breast cancer patients with four cycles [3].

Eligibility criteria for this study included age <80 years, histologically confirmed breast cancer with bidimensionally measurable locally advanced or metastatic disease, no prior chemotherapy for advanced disease (adjuvant chemotherapy was permitted if treatment had been completed more than 6 months prior to study entry), performance status (PS) ≤2, adequate, haematological, hepatic, renal and cardiac functions, and informed consent.

LCM was given as a 1-h infusion at a dose of 18 mg/m^2 every 3 weeks for four cycles. Haematological data were measured weekly and chemical parameters at least before each cycle. If the absolute neutrophil count (ANC) was <1500/μl, treatment was delayed for a week. In an effort to use equitoxic doses, we adjusted LCM to its maximal clinically tolerable level. Tumour response was assessed 3 weeks after the fourth cycle. Patients with response or no change were then followed at monthly intervals. Duration of response was measured from initiation of LCM treatment to progression of disease.

Between July 1990 and September 1992, 22 patients were entered. Median age was 50 years (range 27–75), mean PS 0.7 (range 0–2), the majority were node positive, oestrogen receptor positive, and had received a modified radical mastectomy including axillary dissection with or without radiotherapy. The most common sites of relapse were the liver, lungs, bone and soft tissue, and median duration of relapse was 13 months (range 0–66). Prior therapy was generally radiotherapy or endocrine therapy. 18 patients completed four cycles of LCM, and dose adjustments were made in 6 patients (increased in 2, decreased in 4). The total mean cumulative LCM dose was 69 mg/m^2 (range 58–84).

17 patients were evaluable for response. Reasons for omission were non-measurable disease (2), early death after one cycle (1), rapid progression of hepatic metastases after one cycle (1), and suicide after the second cycle (1). Only 1 patient had a partial response of liver metastases as documented by computed tomography scan which lasted for 6 months (response rate 6%). 8 patients (47%) had no change at re-evaluation. This status persisted for a median duration of 7 months (range 3–11). 8 patients (47%) had progressive disease.

Toxicity was evaluable in 22 patients and was mild and predominantly hematological. In 13 patients with weekly documentation, neutropenia was grade 4 in 8 and grade 3 in 5. One patient had neutropenia grade 4 for 3 weeks, and another was hospitalised for febrile neutropenia. Thrombocytopenia was grade 4 in only 1 patient (no transfusion) and grade 2 in another. Anaemia was rare, but severe in 2 cases with bone metastases. One patient required a blood transfusion. Non-haematologic toxicity was mild. Median overall survival from start of LCM treatment was 11 months. 4 patients are still alive at 24, 25, 26 and 28 months.

The results described for LCM seem to compare unfavourably to those published for free mitoxantrone [4], but the following factors have to be considered. Our patients had a particularly bad prognosis, since median relapse lasted 13 months prior to starting LCM and the proportion with liver metastases was exceptionally high (68%). Pharmacological factors to explain the results may be drug leakage from the liposomal bilayer [5, 6] and inadequate circulation time. These problems may be overcome by the recent development of Stealth liposomes with prolonged circulation times [5–7].

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Correspondence to B.C. Pestalozzi.
The authors are at the Abteilung für Onkologie, Departement für Innere Medizin, Universitätsspital, CH-8091 Zürich, Switzerland.
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