Prednimustine combined with mitoxantrone and 5-fluorouracil for first and second-line chemotherapy in advanced breast cancer

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Summary. A total of 60 patients with advanced breast cancer were treated with a combination of prednimustine (P: 110 mg/m², days 1–5), mitoxantrone (M: 12 mg/m², day 1) and 5-fluorouracil (F: 500 mg/m², day 1) (PMF). Treatment was repeated every 3 weeks. In all 53 patients were evaluable for response. A total of 12 subjects had failed prior chemotherapy for metastatic disease. In response to PMF treatment we observed 21 partial remissions and 3 complete remissions, amounting to a total response rate of 45%. The median duration of response was 39 weeks, and median survival was 56 weeks. Dose-limiting side effects were leukopenia (40 cases) and thrombocytopenia (11 patients). Nausea and vomiting was experienced by 93% of subjects; in 56% of cases it reached WHO stage II–III. Alopecia occurred in 18% of our patients. Our results suggest that PMF represents an active regimen in the treatment of advanced breast cancer and yields a response rate of 45%. Considering that the majority of our patients had not received prior chemotherapy, the question remains open as to whether a 45% response rate outweighs the observed toxicity.

Introduction

Combination cytotoxic chemotherapy is widely accepted for the management of patients with metastatic breast cancer. Depending on patient selection, response rates to first-line drug combinations vary from 40% to 70% [16, 21]. The median duration of response is usually <1 year and the reported median survival of patients with metastatic disease ranges from 18 to 24 months. To date, there is no evidence that any of the cytostatic combination regimens is superior to another, particularly in terms of patient survival. Progress can be made in the development of more efficient drugs as well as in the introduction of less toxic combinations that show at least the same efficacy. In the present study we evaluated a combination regimen consisting of prednimustine, mitoxantrone and 5-fluorouracil (PMF).

Prednimustine is an ester of chlorambucil and prednisolone that has been proven to be effective in breast cancer, producing a low incidence of adverse reactions [10, 15]. The dose-limiting toxicity is myelosuppression (leukopenia and thrombocytopenia), which is reversible and seems to be less pronounced when the drug is given intermittently instead of continuously [12]. Prednimustine appears to be at least as effective as cyclophosphamide and probably causes less toxicity, particularly less alopecia [12, 14].

Mitoxantrone is an anthracenedione whose structure and spectrum of activity are similar to those of doxorubicin [11]. In several randomized trials in patients with breast cancer, mitoxantrone has been compared with doxorubicin, one of the most active single agents against carcinoma of the breast [1, 5]. The response rates and overall survival achieved using the two drugs did not differ significantly. Myelosuppression was the dose-limiting side effect, but the incidence of nausea, vomiting, alopecia, stomatitis, and cardiotoxicity produced by mitoxantrone was much lower than that caused by doxorubicin [1, 17].

One of the most effective combinations used in the treatment of breast cancer is cyclophosphamide, Adriamycin (doxorubicin) and 5-fluorouracil (CAF) [4, 8, 9]. However, combination produces considerable toxicity. Therefore, in the present study prednimustine was substituted for cyclophosphamide and mitoxantrone, for doxorubicin in the hope of finding an effective but less toxic regimen (PMF) for the treatment of advanced breast cancer.

Patients and methods

A total of 60 patients with progressive metastatic breast cancer and measurable or evaluable tumors according to UICC (International Union Against Cancer) criteria were entered in this study. Patients who had previously been treated with anthracyclines or anthrancenediones were
excluded. Before starting treatment, all patients had to have a UICC performance status of ≤3. Other entry criteria included a leukocyte count of >3,500/μl, a platelet count of >100,000/μl and serum bilirubin and creatinine values of <2 mg/dl. Informed consent was obtained before the beginning of PMF therapy. Heart disease or CNS metastases excluded patients from participation in the trial.

Pretreatment laboratory tests included determinations of hemoglobin, leukocyte and platelet counts liver and renal function tests, coagulation profile, serum electrolytes and urinalysis. Leukocyte and platelet counts, hemoglobin values and biochemical profiles were obtained prior to each treatment cycle. Cardiac function was monitored by serial estimations of the left ventricular ejection fraction using multigated analysis. In patients with bone or visceral metastases, chest X-rays and/or abdominal ultrasound examinations were repeated at least every 3 months. Other tests such as bone or computerized tomographic (CT) were used for disease evaluation in individual patients as needed.

The chemotherapy regimen consisted of 110 mg/m² prednimustine given orally on days 1–5, 12 mg/m² mitoxantrone given i.v. on day 1, and 500 mg/m² 5-fluorouracil given i.v. on day 1 (PMF). Treatment courses were repeated every 3 weeks. In case of drug-induced myelosuppression, the dose and/or interval between treatment courses were adjusted. More than 3 weeks' postponement resulted in exclusion from the study due to toxicity. Treatment was discontinued either after a maximum of 12 treatment courses had been completed or if the patient refused further treatment, or if disease progression or severe toxicity occurred.

**Statistical methods.** The data were analysed for frequency, mean and standard deviation of the median, minimal and maximal values, interquartile range and an approximated 95% confidence interval for the median. For the analysis of frequencies a chi-square test was applied; for low frequencies, Fisher’s exact test was used. The survival function was estimated by the Kaplan-Meier product-limit method. Survival was compared using Gehan’s and Peto-Peto’s generalized Wilcoxon test.

**Results**

**Efficacy**

On the 60 patients entered in the study 1 was considered to be ineligible due to CNS metastases. Of the 59 eligible patients, 2 had insufficient data for analysis of response and toxicity; 4 other subjects did not receive >1 treatment cycle (2 refused further therapy, 2 had rapidly progressive disease) and were inevaluable for response but were evaluated for toxicity. The patients' data are described in Table 1.

A median of 6 courses of PMF (range, 3–12) were given. Of 53 patients who were evaluable for response, 3 achieved a complete response (CR), 21 showed a partial response (PR), 21 showed no change and 8 had progressive disease according to UICC criteria. The overall response rate (CR + PR) for all 53 evaluable patients was 45% (95% confidence limits; 32%–59%). The median duration of response in the nine patients who had failed prior chemotherapy and in subjects receiving first-line chemotherapy for metastatic disease was 36 and 41 weeks, respectively.

The median duration of survival was measured from the 1st day of PMF treatment until the day of death in the 53 evaluable patients was 56 weeks (range, 13–71 weeks; 95% confidence limits, 48–64 weeks). Survival was not found to be correlated to prognostic factors determined before the beginning of PMF therapy, such as menopausal status, performance status, disease-free interval, estrogen-receptor status, sites of metastatic involvement and prior treatment.

**Toxic effects**

A total of 57 patients were evaluated for toxic effects according to WHO criteria. In all, 340 courses were given. There were no treatment-related deaths. Leukopenia and thrombocytopenia, evaluated on day 21, were the dose-limiting toxicities. The incidence of hematologic and non-hematologic toxic effects are shown in Table 2.