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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/m^2, days 1–5), mitoxantrone (M: 12 mg/m^2, day 1) and 5-fluorouracil (F: 500 mg/m^2, 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 occured 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 anthracenediones were

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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 urinanalysis. 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/m^2 prednimustine given orally on days 1–5, 12 mg/m^2 mitoxantrone given i.v. on day 1, and 500 mg/m^2 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.

Table 1. Patients' characteristics

Patients (*n*)	Entered	Evaluable for toxicity	Evaluable for response
Total	60	57	53
Median age (range): 58 (39–75 years)			
Menopausal status:			
Premenopausal	20	18	17
Postmenopausal	40	39	36
Hormone receptor status:			
Estrogen receptor positive	13	13	12
Estrogen receptor negative	21	20	17
Estrogen receptor unknown	26	24	24
Performance status:			
0	9	9	9
1	27	25	25
2	21	21	18
3	3	2	1
Dominant site of disease:			
Soft tissue/nodes	10	10	10
Bone	19	18	17
Visceral	30	28	25
Advanced primary lesion	1	1	1
Number of metastatic sites:			
1	25	24	24
2	21	20	20
3	10	10	8
>3	4	3	1
Prior therapy:			
Chemotherapy (CMF regimen)	17	14	12
Adjuvant	5	3	3
For metastases	12	11	9
Hormone therapy	21	21	20
Radiotherapy	39	37	34

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 from the 1st day of treatment until the detection of progressive disease was 39 weeks (range, 17–99 weeks; 95% confidence limits, 30–48 weeks). Responses were seen at all sites of metastatic involvement and no significant differences were observed: lung, 39% of patients (7/18); pleura, 40% (2/5); liver, 33% (2/6); bone, 30% (6/20); and soft tissue/nodes, 54% (15/28).

Patients receiving PMF after having failed prior chemotherapy for advanced disease showed a 33% overall response rate (3 of 9 patients) as compared with 48% (21 of 44 subjects) for those receiving PMF as first-line chemotherapy for metastatic disease. The median duration of response in the nine patients who had failed prior chemotherapy and in subjects receiving first-line treatment were 36 and 41 weeks, respectively.

The median duration of survival as 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.

Table 2. Toxic effects

Toxic effects	WHO grade	0	I	II	III	IV
Anemia		33 (4)[a]	17 (5)	7 (5)[b]	0	0
Leukopenia		18 (2)[a]	32 (6)[a]	3 (3)	4 (3)[a]	0
Thrombocytopenia		46 (12)[c]	7 (0)	3 (2)	1 (0)	0
Stomatitis		55 (14)[c]	0	0	1 (0)	1 (0)
Diarrhea		54 (13)[c]	1 (0)	1 (1)	1 (0)	0
Nausea/vomiting		4 (0)	21 (8)[a]	22 (5)[b]	10 (1)	0
Cutaneous reactions		56 (14)[c]	1 (0)	0	0	0
Hair loss		22 (5)[a]	25 (8)[b]	8 (1)	2 (0)	0
Cardiac abnormality		53 (13)[c]	3 (1)	0	1 (0)	0
Fever		53 (11)[b]	3 (2)[a]	1 (1)	0	0

Data represent the number of patients affected from a total of 57 evaluable subjects. Values in parentheses indicated the number of patients who underwent prior CMF therapy

[a] One patient pretreated with adjuvant CMF therapy
[b] Two patients pretreated with adjuvant CMF therapy
[c] Three patients pretreated with adjuvant CMF therapy

In 8 patients, postponement of treatment for >3 weeks resulted in exclusion from the study due to a WBC count of <3,000/μl and/or a platelet count of <75,000/μl at scheduled treatment times (after courses 5 and 7 in 2 cases and after courses 6, 9, 10 and 11 in 1 subject, respectively). In two of these eight patients, invasion of the bone marrow related to disease progression could be proven by bone-marrow aspiration or biopsy. In six cases, cumulative myelotoxicity for PMF has to be assumed. One of these six patients had been pretreated with CMF and two had received prior chest-wall irradiation following mastectomy. In one of these subjects we observed cumulative thrombocytopenia; in another we noted cumulative leukopenia; and in the other four, cumulative leuko- and thrombocytopenia was seen. The dominant site of disease in one of these patients was the liver, that in four subjects involved bone metastases and that in another case, multiple pulmonary metastases.

To determine whether a dose-response relationship existed, we carried out a correlation between hematologic toxicity and the response category. It is conceivable that hematologic toxicity reflects the amount of cytotoxic drugs that are available to the cells. To accomplish such an assessment over the whole treatment periods. We categorized each measurement of WBC and platelets into WHO grades and determined the mean grade for the entire treatment period for each individual patient. Among the patients with a mean WBC grade of more than 0, 51% responded to PMF as compared with 29% of those who did not develop leukopenia at any time. Of the patients with thrombocytopenia, 71% showed an objective response as compared with 40% of those who did not develop thrombocytopenia during the whole treatment period. It seems that in some patients treated with PMF, dose escalation would have been desirable so as to achieve a higher response rate. On the other hand, eight patients experienced prolonged myelosuppression that caused postponement of therapy for >3 weeks, resulting in their removal from the study.

Cardiac abnormalities developed in four patients during treatment. This was related to disease progression in two cases (malignant pericardial effusion). One patient was found to have an asymptomatic decrease in cardiac ejection fraction when treatment was discontinued due to disease progression (a decrease from 62% to 55% in the left ventricular ejection fraction after 10 courses of PMF) and another showed clinical evidence of heart failure, which was ascribed to chemotherapy (a fall in the left ventricular ejection fraction from 66% to 37% after the maximally planned total of 12 courses had been completed without dose reduction). The latter patient responded to therapy with digitalis and diuretics. In neither case was any predisposing factor for heart disease identified.

Discussion

The present study indicates that PMF is of therapeutic value in both pretreated and previously untreated patients with advanced breast cancer. The overall rate of response (CR + PR) to PMF was 45% and the median duration of response was 39 weeks. Considering only subjects who received PMF as first-line therapy, the 48% response rate and the median duration of response of 41 weeks are similar to the results reported by several other authors who used CAF as first-line chemotherapy in randomized trials [3, 6, 19]. The latter investigators observed response rates ranging between 41% and 64% and a median duration of response of 27–52 weeks.

For comparison, some investigators have substituted mitoxantrone (Novantrone) for Adriamycin in the CAF regimen [3, 6, 13]. This so-called CNF protocol resembles our PMF combination more closely than it does the CAF regimen. Most previously published data on CNF (cyclophosphamide, mitoxantrone, 5-fluorouracil) in advanced breast cancer show response rates (36%–42%) and median durations of response (20–34 weeks) that are lower than those observed in our study using PMF.

When we started the present study, we hoped that the PMF regimen would produce fewer side effects than CAF and other similar protocols. However, our results show that the observed toxicity was very similar. In eight of our patients we observed prolonged myelosuppression that caused postponement of therapy for >3 weeks, resulting in the removal of these subjects from the study. Stuart-Harris and co-workers [20] observed prolonged thrombocyto-

penia requiring discontinuation of mitoxantrone in three patients with extensive liver metastases who had undergone >6 months of treatment with this drug. Only one subject had received prior chemotherapy. Bone marrow aspiration revealed normal values in two of these cases. As in most other reports, cycle-by-cycle myelotoxicity data were not provided for assessment of the possibility of cumulative toxicity. In 52 patients treated with MCF (mitoxantrone, cyclophosphamide and 5-fluorouracil) as first-line therapy, Holmes et al. [7] observed that the lowest recorded platelet count in courses 3 and 6 was significantly lower than that in course 1, suggesting cumulative thrombocytopenia; only 6 of these patients had extensive liver involvement. Granulocytopenia was dose-limiting in the study by Holmes et al., but there was no evidence of cumulative myelotoxicity. Pharmacokinetic studies in patients with hepatic impairment or third space have shown that the average total clearance of mitoxantrone was less than half of that found in patients with normal liver function, and the average terminal half-life was almost doubled [18]. A recent publication has suggested that there is a leukaemogenic potential for prednimustine given at similar doses in combination therapy for advanced breast cancer [2]. This should also be borne in mind by physicians who use a PMF regimen.

In summary, PMF is an active combination for first- and second-line chemotherapy of advanced breast cancer. Although a comparison of PMF with previously published data on CAF and CNF is difficult in the absence of a randomized study, the objective response and duration of response obtained in similar groups of patients are similar to those found in the present study using PMF. The question as to whether the observed response rate outweighs the observed toxicity remains open.

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