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Ifosfamide combination chemotherapy in advanced breast cancer*

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Summary. The objective of our clinical studies was to develop an effective combination chemotherapy regimen (CHT) with acceptable side effects, consisting of the two most potent drugs used as single agents in breast cancer. We tested the combination of an anthracycline, epirubicin (A) at 70 mg/m^2 i.v. on day 1 or (B) at 120 mg/m^2 i.v. on day 1 with an alkylating drug ifosfamide (IFO), (C) at 2.5 g/m^2 in an i.v. infusion given over 4 h on days 1–3 or (D) at 5 g/m^2 in a 24-h i.v. infusion given on day 1. Courses were repeated every 4 weeks. The combinations were given as first-line therapy as follows: CHT (A, C) in six cases and CHT (B, C) in five cases of advanced breast carcinoma, and CHT (B, D) in seven patients with primary inflammatory breast cancer. Due to side effects (e.g., stomatitis, mental disturbances) and applicability, CHT regimen (B, D) was preferred. Responses (12/18) occurred 1–3 cycles earlier than those previously achieved using the conventional epirubicin/cyclophosphamide CHT. We conclude that 5 g/m^2 IFO given i.v. over 24 h with uroprotection (mesna) in a two-drug regimen is an effective dose with tolerable toxicity. Alopecia was seen in all cases. However, according to our experience, myelotoxicity is the dose-limiting factor for both of these drugs.

Introduction

Widely different approaches may be used for palliative treatment of metastatic breast cancer, according to a Consensus Development Conference held in July 1988 in Germany [12]. In this disease, the end point for physicians should be the attempt to achieve maximal palliation of the symptoms with minimal toxicity for as long as possible. Besides confirmation of the response to treatment, for clinical trials the best objective measure of efficacy is the time to progression.

Adriamycin given in combination with an alkylating agent, e.g., cyclophosphamide, is an effective standard regimen for the treatment of metastatic breast cancer [14]. In recent years, further developments have been undertaken to improve the effectiveness and reduce the objective and subjective toxicities of both groups of drugs. As a result Adriamycin may be replaced by epirubicin [2, 8] and ifosfamide (IFO) may be substituted for cyclophosphamide [1, 3, 4, 7, 11, 18], as both have been shown to be effective as single agents or in combination with other drugs in metastatic breast cancer treatment [10].

The objective of our clinical phase II trial was to analyze combinations of low- and high-dose epirubicin and IFO given at various times and to assess their objective and subjective toxicity as well as their therapeutic activity in terms of complete and partial responses.

The follow-up time of this trial is rather limited; therefore, this analysis does not include response duration or survival data.

Patients and methods

Drugs. IFO at two different doses and times of administration was combined with two different doses of epirubicin given as a bolus injection (see Table 1). Depending on the dose of IFO, mesna [5, 6, 13, 15, 16] was given at different times for uroprotection. For antiemetic treatment, Decadron and Alizapride plus biperiden were given (Table 2).

Patients. A total of 18 patients with advanced breast cancer were treated with three different epirubicin-IFO chemotherapy regimens.

Evaluation. For evaluation of objective response, UICC (International Union Against Cancer)-criteria were applied [9]. A complete response (CR) was defined as the disappearance of all measurable lesions for at least 2 months. A partial response (PR) was defined as a reduction of >50% in the size of the tumor and the absence of new lesions for at least 2 months. No change (NC) was defined as stabilization of disease or a reduction of <50% in tumor parameters, with no progression of other

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Table 1. Cytostatic chemotherapy regimens

Regimen	Drug	Dose	Administration
A	Epirubicin	70 mg/m²	i. v. bolus, day 1
B	Epirubicin	120 mg/m²	i. v. bolus, day 1
C	IFO + mesna	2.5 g/m²	i. v., 4-h infusion, days 1–3
D	IFO + mesna	15.0 g/m²	i. v., 24-h infusion, day 1
Repeat every 28 days			

Table 2. Supportive care during IFO-epirubicin combination chemotherapy

Uroprotection:
4-h IFO infusion
mesna (0.5 g/m², i. v. bolus, at 0, 4, 8, and 12 h after IFO)

24-h IFO infusion
mesna (2.5 g/m² i. v. for 24 h and 2.5 g/m² i. v. for 8 h on day 2 after IFO)

Antiemetic treatment:
Decadron phosphate (12 mg i. v. bolus before epirubicin administration)

Alizapride (400 mg/m² i. v.) plus biperiden (5 mg i. v.) 24-h infusion, days 1 and 2

lesions for at least 3 months. Progression of disease (PD) was defined as an increase of >25% in any of the metastatic lesions. Toxicity was evaluated according to WHO criteria [17].

Results and conclusions

A total of 18 patients with advanced breast cancer were treated according to the new epirubicin-IFO combination regimen. After the first four cycles of chemotherapy, response was analyzed according to the maximal duration of response; hematological and other major toxicities were also assessed.

Table 3 shows the results for different doses of epirubicin given with doses of 2.5 and 5 g/m² IFO. PRs were attained by 3/6 patients after 2–3 cycles of low-dose epirubicin chemotherapy (A). In contrast, 3/5 patients treated with the high-dose epirubicin-regimen showed a PR. A higher response rate (6/7 patients) was seen after treatment with 120 mg/m² epirubicin given on day 1 as an i. v. bolus (B) and 5 g/m² IFO given on day 1 as a 24-h infusion (D). The latter, easily practicable high-dose regimen was also given to six patients with malignant uterine tumors and was effective in four cases. In one case (liposarcoma), a CR could be proven by second-look laparotomy.

It is obvious that responses occurred 1–2 cycles earlier with the present regimen in comparison with an epirubicin (B)/cyclophosphamide (600 mg/m² i. v.) regimen. In only 6 of 17 patients was a PR seen after the second cycle of chemotherapy; however, this was related to hematological and other major toxicities. In terms of the time to the best response, the median number of polychemotherapy cycles was 1.5 for the BD regimen, 2 for the AC/BC combination, and 3 for the conventional regimen comprising epirubicin and cyclophosphamide. Primary PD of around 15% was seen in all subgroups.

Table 3. Response and toxicity of 2.5–5 g/m² IFO-epirubicin combination chemotherapy in 18 patients with advanced breast cancer

Regimen	Patients (*n*)	Response: Chemotherapy cycles (*n*)			
		1	2	3	4
AC	6	-	2× PR 1× PD	1× PR	2× NC
BC	5	-	3× PR	1× NC 1× PD	
BD	7[a]	5× PR	1× PR 1× PD		

[a] Three patients had primary stage T4 disease with no distant metastases

The main toxicities were alopecia in all patients, moderate nausea and vomiting, and stomatitis (AC/BC/BD regimen: 6/18). Mental disturbances were observed in two elderly women receiving the IFO regimens. The dose-limiting factor for all IFO regimens was myelotoxicity (WHO grade 4 was seen only in patients >60 years of age). The question as to whether the high response rates obtained with the BD regimen correlate with a longer time to progression cannot be answered, as the number of cases was too small and the observation time, too short.

Especially for primary stage T4 lesions, the new combinations with IFO proved to be more effective than conventional cyclophosphamide regimens, thus enabling early surgical treatment and resulting in less psychological stress for these patients due to the remission of their disease. Although these high-dose IFO combination regimens are toxic, they do show activity in breast and uterine tumors. Considering the high rate and rapid achievement of responses, particularly if they prove to be long-lasting, the present regimens show promise for the future management of breast cancer.

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