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A phase II study of intensive-dose epirubicin/verapamil as induction therapy followed by intensive-dose ifosfamide for advanced breast cancer*

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Summary. Preliminary data of an ongoing phase II-study in metastatic breast cancer patients are presented. Patients with metastatic breast cancer entered the study after hormone therapy had failed; prior treatment with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) was also allowed. The patients were treated with three cycles of 40 mg/m^2 epirubicin i.v. on days 1–3 and 4 × 120 mg oral verapamil on days 0–3, given every 3–4 weeks. After three chemotherapy courses, ifosfamide was given as a short infusion of 3 g/m^2 on days 1–3. Mesna (20% of the total ifosfamide dose) was given 0, 4 and 8 h after ifosfamide administration. Response was evaluated after three cycles of epirubicin/verapamil and after the last (third) cycle of ifosfamide. The side effects of this treatment were tolerable. The epirubicin/verapamil combination was no more toxic than epirubicin alone. Despite the high dose of verapamil, systolic blood pressure remained above 80 mm Hg, and patients never had a period of strict bed rest. Alopecia was almost complete after induction therapy with epirubicin/verapamil, and nausea and vomiting were absent or mild during epirubicin/verapamil chemotherapy and were easily controlled by antiemetics during ifosfamide treatment. Stomatitis and mucositis, the main toxic effects, could be ameliorated by intensive mouth-washing procedures. The haematological toxicity was greater after epirubicin/verapamil treatment than after ifosfamide therapy, but neither bleeding nor infections due to thrombocytopenia or leucopenia were observed.

Introduction

Breast cancer is the most common malignancy in women [2]. The prognosis depends mainly on the stage of disease at the time of diagnosis. Patients with metastatic breast cancer are incurable [25]; even when complete remission (CR) is achieved, relapse is inevitable [22].

Chemotherapy has been established as an effective tool for palliation in metastatic breast cancer. The most common polychemotherapeutic regimens are CMF (cyclophosphamide, methotrexate and 5-fluorouracil), VAC (vincristine, doxorubicin and cyclophosphamide), and FAC (where vincristine is replaced by 5-fluorouracil). There is no difference in overall survival of responsive patients between these treatments of different intensity [26]; even the quality of response seems to have only minor influence on overall survival [10]. For palliative purposes, some investigators have recommended a less intensive approach to the therapy of metastatic breast cancer [13, 39]. This could, however, lead to the abandonment of efforts to develop curative treatments and failure to try better regimens, even if they are not curative.

At the NCI of Milan it has been shown that the response rate among patients receiving >85% of the planned CMF dose was almost twice that observed when <65% of the planned dose was given [5]. Hence, there is considerable evidence for a dose-related response in the treatment of breast cancer and high-dose studies should be done.

Epirubicin is an effective agent for the treatment of advanced breast cancer (Table 1). Most of the patients in previous studies had metastatic breast cancer refractory to prior therapy. In most studies epirubicin has been given at a dose of 60–90 mg/m^2 as a bolus injection. Data concerning prior chemotherapy revealed a response rate of 22% for patients who had received prior chemotherapy and that of 62% for previously untreated patients. In comparison, doxorubicin response rates were generally very similar [8, 31], but epirubicin may have a higher therapeutic index [4, 7].

Multidrug resistance is an important problem of chemotherapy. It has been established that the development of resistance against one anthracycline leads to cross-resistance to others, including the vinca alkaloids, although the two groups of drugs are quite different in their chemical structure and their known mechanisms of action. This

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Table 1. Epirubicin activity in advanced breast cancer

Authors	Dose	Patients (*n*)	CR	PR	R %
Hurteloup et al. [29]	75 mg/m^2	28	1	8	32
Rozencweig et al. [38]	90 mg/m^2	34	0	9	27
Kolaric et al. [34]	80–100 mg/m^2	13	2	3	38
Young et al. [43]	85 mg/m^2	24	0	6	25

CR, complete response; PR, partial response; R, response rate

Table 2. Ifosfamide monotherapy as first-line treatment

Authors	Dose schedule	Patients (*n*)	CR	PR	R %
Ahmann et al. [1]	4 g/m^2, day 1, every 3 weeks	20	0	4	20
Brema et al. [9]	0.6 g/m^2, days 1–5 every week	22	3	6	40
Falkson and Falkson [21]	40 mg/kg, day 1 every week	27	2	12	52

CR, complete response; PR, partial response; R, response rate

Table 3. Criteria for exclusion of patients from this study

Age, >75 years; life expectancy, <6 months
Karnofsky Index, <70%
Hormone treatment or chemotherapy during the previous 4 weeks
Pretreatment with anthracyclines
Previous or concurrent malignancy other than breast cancer
WBC count of <3.0/nl; platelets, <100/nl
Serum creatinine, >1.3 mg/dl
Creatinine clearance, <60 ml/min per 1.73 m^2
Bilirubin, >1.5 mg/dl
Only pleural infusions, ascites or bone lesions
Brain involvement or leptomeningeal disease
Presence of another non-malignant disease that is incompatible with the protocol
Uncontrolled or potentially active site of infection
Expected difficulties in follow-up

Table 4. Patient characteristics

Patients treated	7
Median age (range) (years)	50 (32–66)
Pre-/postmenopausal	3/4
Performance status (WHO):	
0–1	6
2–3	1
Organ systems involved (*n*):	
2	2
3	4
>3	1

cross-resistance can also be induced when a vinca alkaloid is given first [14–17]. Anthracyclines are rapidly accumulated in cells and bound to the DNA in the nucleus [35, 40]. In resistant cells, the accumulation was found to be decreased, which may be one of the mechanisms of resistance [18, 19, 34, 39]. In 1976, Juliano and Ling [32] described the presence of increased amounts of a glycoprotein with an approximate molecular weight of 170 kDa in multidrug-resistant cells. They called it P-glycoprotein, and it seems to be involved in a transport system responsible for extrusion of drugs from multidrug-resistant cells [23, 33].

It has been demonstrated that multidrug resistance can be counteracted by inhibition of the active outward transport of the drug, which can be achieved by competitive inhibition with analogues to the transported drug [30] and treatment with calcium transport blockers such as verapamil [20, 36, 37, 41, 42]. Furthermore, verapamil inhibits binding of vinblastine analogues to P-glycoprotein in membranes [12] and increases the ATPase activity of purified P-glycoprotein [24]. The counteraction of multidrug resistance by verapamil does not seem to be due to its effect on calcium transport [28].

In several studies, ifosfamide has been shown to be active in monotherapy of disseminated breast cancer (Table 2). In previously untreated patients with metastatic breast cancer and viscerally dominant disease, an objective response rate of 40% was observed [21]. The cumulative objective response rate for ifosfamide monotherapy in advanced breast cancer was 45% (including a 15% complete remission rate). These data are based on 223 evaluable patients, most of them pretreated with polychemotherapy. Less strict response criteria in the past may have contributed to this optimistic result. Response rates for ifosfamide are comparable with those for cyclophosphamide, but the therapeutic index of ifosfamide is better than that of cyclophosphamide because of the former drug's reduced side effects and lower haematological toxicity [6].

Patients and methods

The exclusion criteria applied to this study are shown in Table 3. All patients who had received chemotherapy more than 4 weeks before and whose regimens did not contain anthracyclines were eligible for this study, regardless of whether they had undergone previous chemo- or hormone therapy. All patients had measurable and advanced disease at the time of entry into the study.

Patients were treated with three cycles of 40 mg/m^2 i.v. epirubicin on days 1–3 and 4 × 120 mg oral verapamil on days 0–3, given every 3–4 weeks. After three chemotherapy courses, ifosfamide was given as a short infusion of 3 g/m^2 on days 1–3. Mesna (20% of the total ifosfamide dose) was given 0, 4 and 8 h after ifosfamide administration. Response was evaluated after three cycles of epirubicin/verapamil and after the last (third) cycle of ifosfamide. Seven patients completed the first three chemotherapy courses; two of them also received three cycles of ifosfamide and the remaining patients, up to two cycles. Patient characteristics are shown in Table 4.

Table 5. Treatment response in seven patients after three courses of epirubicin/verapamil

CR	1
PR	2
NC and MR	2
PD	2

CR, complete response; PR, partial response; NC, no change; MR, minimal response; PD, progressive disease

Table 6. Toxicity of epirubicin/verapamil in seven patients after three courses

Median platelet count	125.0/nl
Median WBC count nadir	1.5/nl
Mucositis (WHO grade 2–3)	7
Mucosal bleeding	1
Systolic hypotension (80–100 mm Hg)	4
AV block I°	1

AV, atrioventricular

Results

Seven patients completed induction therapy with high-dose epirubicin and verapamil. In one case, complete remission could be documented; in two cases, partial remission; and in two others, stable disease (Table 5). The toxicity of intensive-dose epirubicin and verapamil was tolerable (Table 6). All patients developed complete alopecia and varying degrees of mucositis. Neither bleeding nor infection due to haematological toxicity occurred; the median platelet count was 125/nl and the median WBC count nadir was 1.5/nl. In four patients, systolic blood pressure was between 80 and 100 mm Hg; however, in only one patient was an atrioventricular (AV) block I° on the ECG during verapamil therapy, and no patient had to stay in bed because of hypotension.

Two patients also received three cycles of ifosfamide, one of whom achieved a partial remission. In this patient, treatment with intensive-dose epirubicin/verapamil and intensive-dose ifosfamide resulted in a steep decrease in CA 15/3 blood levels (Fig. 1). The second patient who received ifosfamide 1 had a large tumour load; the whole ventral thoracic wall was involved and metastases were found in the pleura, bone and local lymph nodes. In this patient there was a tumour regression of <50%, which was interpreted as a minimal response. The accompanying decrease in CA 15/3 blood levels was less impressive than that observed in the other patient (Fig. 2).

The main side effects of ifosfamide were nausea and vomiting, which could be reduced by antiemetics such as haloperidol or triflupromazine hydrochloride. The hematological toxicity of the last three courses of chemotherapy was less marked than that of the first cycles; with a platelet count above 100/nl, no transfusions were needed. Due to mesna administration, no urotoxicity occurred. Signs of encephalopathy due to ifosfamide therapy were not observed.

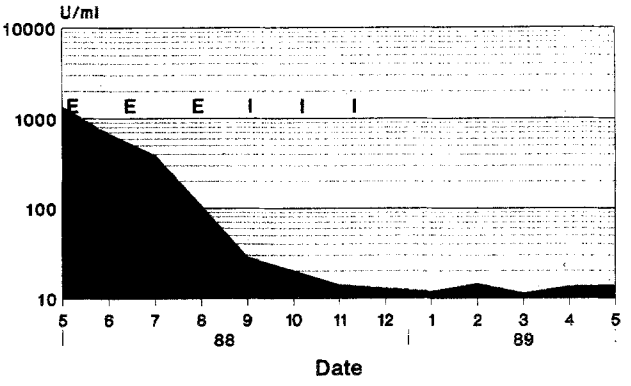

Fig. 1. CA 15/3 blood levels in one patient who showed a partial response after three courses of intensive-dose epirubicin/verapamil (*E*) followed by intensive-dose ifosfamide (*I*). Normal value, <25 units/ml

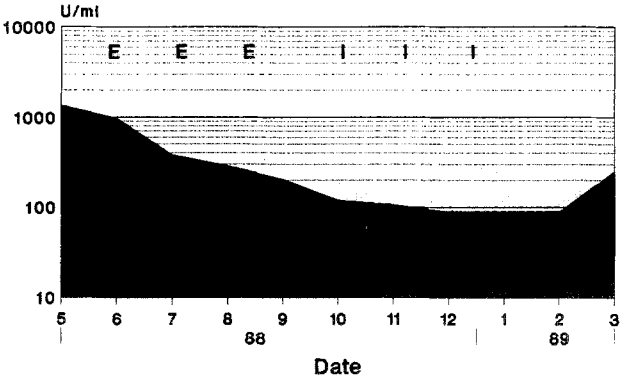

Fig. 2. CA 15/3 blood levels in a patient who showed a minimal response after three courses of intensive-dose epirubicin/verapamil (*E*) followed by intensive-dose ifosfamide (*I*). Normal value, <25 units/ml

Discussion

For a long time the use of ifosfamide was limited by its urotoxicity. Now that this side effect can be controlled by mesna, there is new interest in this drug, and successful regimens have been reported [3].

It is too early for an evaluation of the present regimen. After therapy using intensive dose-epirubicin in combination with the chemosensitizer verapamil and the non-cross-resistant drug ifosfamide, high cytostatic activity might be expected, since it has been demonstrated that response rates correlate with dose intensity in breast cancer [11, 27]. Overall, three of seven patients achieved a remission, two stabilized and in two patients the disease progressed after induction therapy with epirubicin and verapamil. The toxic side effects of this regimen were tolerable. This study will be continued; in the meantime, ifosfamide is recommended for further evaluation in metastatic breast cancer.

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