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CLINICAL TRIAL REPORT

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Phase II study of second-line treatment with high-dose cyclophosphamide in recurrent metastatic breast cancer

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Abstract A total of 78 patients with second recurrence or progression of histologically verified breast cancer were treated with single-agent cyclophosphamide given at 2.5 g/m^2 by i.v. infusion every 3 weeks along with mesna support. All had previously been treated with epirubicin and cisplatin or epirubicin alone. Toxicity was predominantly hematologic: WHO grade III + IV toxicity was found in 95% of cases. The overall response rate was 26.7% (95% confidence limits, 15.8–41.4%), with 7% of patients achieving a complete response (CR) and 19.7%, a partial response (PR). The median duration of CRs and PRs was 11 and 5 months, respectively. The response rate observed for patients previously treated with epirubicin alone was 30.5% in contrast to the 8.3% recorded for patients previously treated with cisplatin plus epirubicin. Thus, an indication of cross-resistance was absent between cyclophosphamide and epirubicin but possible between cyclophosphamide and cisplatin.

Key words Metastatic breast cancer · Cyclophosphamide

Introduction

The prognosis of patients with stage IV breast cancer is dismal. Although the majority of such patients respond to conventional chemotherapy, virtually all suffer a relapse. The median duration of survival for this group is approximately 18–24 months.

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The activity of several cytotoxic agents in different groups has been investigated in breast cancer [1, 2]. Anthracyclines and alkylating agents are probably the most active antineoplastic drugs. Cyclophosphamide (CTX) is the most well-investigated alkylating drug. Given as a primary treatment, CTX induces remission in 30–35% of a population of patients with recurrent breast cancer, with the median response duration being 4 months [3]. Responses lasting as long as 9–14 months have been reported. However, a complete remission is seldomly obtained in more than 5% of cases [4].

As estimated form the data existing thus far, it seems possible only in a modest degree to improve these results by adding other cytotoxic drugs. In a randomised trial, Rubens et al. [5] found continuous peroral treatment with CTX at 200–300 mg day to be equivalent to an intermittent combination regimen of Cyclophosphamide, Metothrexote and Fluorouracil (CMF) plus vinblastine, obtaining a response rate of 55%. In other trials [6, 7] the difference between combination chemotherapy and single-drug treatment in advanced breast cancer is small or lacking. The toxicity of most drugs is predominantly myelosuppressive and as a consequence, doses of the individual drugs in a combination regimen have to be reduced.

In breast cancer and other malignancies that are sensitive to chemotherapy, it has been shown that the antineoplastic effects of CTX are dose-dependent [8, 9]. This could be explained by the assumption that high-dose treatment may overcome resistance in subclones. The retrospective analysis made by Hryniuk, et al. [10] of dose intensity for chemotherapy in advanced breast cancer and the review article by Hryniuk and Bush [11] suggest the importance of dose intensity in metastatic breast cancer. Focan et al. [12] revealed a dose-response relationship of epirubicin-based first-line chemotherapy for advanced breast cancer in a prospective trial. The results obtained by Peters' group [13] with myeloablative chemotherapy and stem-cell support in recurrent breast cancer support these data. In

a study in mice, Klein et al. [14] found that doses of CTX could be increased without increasing toxicity when drug delivery was extended to a continuous 24-h infusion, and the therapeutic effect was even improved.

In a randomized phase II study of CTX versus ifosfamide in soft-tissue sarcomas [15], 17/30 previously untreated patients and 16/23 previously treated patients experienced WHO grade 3–4 hematologic toxicity when treated with CTX given at 1.5 g/m^2 as a 24-h infusion every 3 weeks. In a study including patients with metastatic-cell lung cancer, Thatcher et al. [16] applied increasing dose levels of intermittent high-dose CTX: 1.5, 2.5, and 3.5 g/m^2, respectively. Although higher doses caused increasing myelosuppression, it was not necessary to diminish the dose intensity by either reducing the drug dose of prolonging the treatment interval. Thus, all hematologic parameters recovered within 3 weeks. Generally, the tolerability was high. The median leukocyte nadir count was 1,100/μl in a phase II study of CTX given at 2.5 g/m^2 every 3 weeks as a 24-h infusion in advanced non-small-cell lung cancer [17]. No advantage for the infusion schedule over a conventional bolus regimen was found at this dose level.

The present phase II study was intended to evaluate the efficacy of high-dose CTX given at 2.5 g/m^2 every 3 weeks as a 24-h infusion in recurrent breast cancer previously treated with epirubicin and cisplatin or epirubicin alone. Experimental and clinical data do not support that cross-resistance between anthracyclines and CTX exists. However, the knowledge of cross-resistance between cisplatin and CTX is poorly elucidated [18], and the present study was secondarily focused on this subject.

Patients and methods

Patients with histologically proven measurable or assessable recurrent and progressive breast cancer were eligible. All patients had previously been treated with the anthracycline epirubicin. Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2, a minimal life expectancy of ≥ 2 months, an upper age limit of 70 years, a WBC count of $\geq 3{,}000$ μl, and a platelet count of $\geq 100{,}000$ μl unless due to bone marrow carcinomatosis. Serum Ca and serum creatinine levels had to be below 2.74 mmol/l and 130 μmol/l, respectively. Informed consent was obtained from all patients. Patients with brain metastases or previous malignant diseases were not eligible. Alkylating agents except for cisplatin must not have been used previously, unless as adjuvant therapy for more that 12 months prior to entry into the study. One or more indicator lesions had to be outside previously irradiated areas, and prior radiotherapy, hormone therapy, or chemotherapy should not have been given within 3 weeks prior to entry into the study. More extensive radiation treatment compromising bone marrow function was not accepted.

Treatment plan

Eligible patients were treated with CTX given at 2.5 g/m^2 over 24 h via i.v. infusion every 3 weeks along with mesna given at 700 mg/m^2 immediately before and five times during cytotoxic treatment. All patients received hydration with 1 l 5% dextrose with saline followed by 500 ml 15% mannitol before the start of the CTX infusion. During treatment, hydration was continued with 2 l 5% dextrose with saline.

Patients demonstrating excessive marrow suppression (a nadir WBC count of $< 1{,}000$ μl and/or a platelet count of $< 50{,}000/\mu$l) had their dose of CTX reduced on subsequent courses to 67% of the planned level. Drug administration was postponed for 1 week if the WBC at the time of retreatment was $< 2{,}000$ μl or the platelet count was $< 100{,}000$ μl. If full recovery had not occurred at 2 months after the last dose of CTX, patients went off study. The dose was escalated by 24% if hematologic toxicity was less than WHO grade 2. Treatment was to be continued until disease progression of severe toxicity developed, whatever came first. Treatment was discontinued if there was disease progression after two treatment cycles.

A history and physical examination with assessment of the evaluable lesions, WHO performance status, and blood chemistry were repeated before each cycle. Complete blood counts were also determined weekly between cycles.

Tumour response

Patients were availabe for response if they had completed at least three courses of therapy, unless there was rapid early progression. The response criteria were as follows. A clinical complete response required the disappearance of all measurable or assessable disease as well as all signs, symptoms, and biochemical changes related to the tumor for longer than 4 weeks, during which time no new lesion could appear. A clinical partial response required that, as compared with pretreatment measurements, the lesion showed a reduction in size of more than 50% of the sum of the perpendicular diameters of all measurable lesions that lasted for more than 4 weeks, during which time no new lesion could appear or no existing lesion could grow. Parients demonstrating stable disease were considered to be nonresponders. Progression was defined as a 25% increase in lesion size or the appearance of new lesions. The response duration in patients achieving a complete response was recorded from the time the response was documented. The duration of a partial response and of stable disease was recorded from the time of the start of treatment.

Results

A total of 78 patients were registered in this study and 71 were considered eligible. Their median age was 55 (range, 29–69) years. In all, 3 were premenopausal and 68 were postmenopausal, either because of age or due to previous treatment. In 4 cases the estrogen-receptor status was unknown, in 40 cases it was negative, and in 27 it was positive.

A total of 34 patients had preivously been treated with a CTX-based adjuvant regimen [CMF ($n = 30$) or CEF, (Cyclophosphamide, Epirubicin and Fluorouracil), ($n = 4$)] for a median of 30 (range, 12–144) months. All of these were randomized to treatment with epirubicin (59 patients) or epirubicin and cisplatin (12 patients) after their first relapse. The median interval since previous cytotoxic treatment for metastatic disease was 3 (range, 1–48) months. Only two patients had a very long-lasting remission (48 months) before the start of second-line cytotoxic treatment with CTX.

One patient had a partial remission for 6 months and the other showed no change. Altogether 36 patients were previously treated with antiestrogens either in the adjuvant setting (5), for metastatic disease (28), or both (3). Lesions were localized mainly in the lungs, liver, and bones. The patients' characteristics are summarized in Table 1.

In all, 7 patients were not eligible for the following reasons: previous treatment with CTX ($n = 3$), another malignant disease ($n = 1$), receipt of an adjuvant CTX-based regimen within 12 months of the start of treatment ($n = 2$), and the absence of measurable or assessable lesions ($n = 1$). A total of 460 courses were given. The patients received a median of 5 (range, 1–24) courses each; 90% received ≥ 3 courses of therapy and 52% received > 6 courses.

Toxicity

Three patients (4%) died of toxicity: one with pulmonary edema caused by acute water-retention syndrome and two with septicemia. The main and dose-limiting toxicity was hematologic, with 48 patients experiencing hematologic toxicity of WHO grade IV; 17, that of grade III; and 6, that of grade II (Table 2). Two-thirds of the patients were treated with 100% of their planned doses; 4 (5.6%) received dose escalations to 125% of the planned level, whereas 27% were reduced to 67% doses. The hematologic toxicity was predominantly exerted on leukocytes; 93% of patients developed only grade I–II thromobocytopenia. Hematopoietic growth factors were not used to prevent or treat toxic granulocytopenia. The majority of patients had grade 2–3 nausea and vomiting. Total alopecia appeared in all cases. There was no evidence of hemorrhagic cystitis or other urologic toxicity. Despite the pronounced toxicity, the treatment was generally well tolerated.

Table 1 Patients' characteristics (*ERT* Estrogen receptor)

Number of patients	78
Eligible	71
Median age (range)	55 (29–69) years
Number of metastatic lesions:	
1	26
2	36
≥ 3	16
Dominant site of disease:	
Soft tissue	11
Bone	14
Visceral	53
Prior treatment:	
(1) Adjuvant chemotherapy	34
(2) Adjuvant antiestrogen	5
(3) Antiestrogen for metastatic disease	28
(4) Epirubicin	59
(5) Epirubicin + cisplatin	12
(1) + (4) and (1) + (5)	31
Receptor status:	
ER-positive	34
ER-negative	40
Unknown	4
Menopause status:	
Premenopausal	3
Postmenopausal	75

Response

Of the 71 eligible patients, 14 were not evaluable for response, in 8 cases due to early death caused by hepatic failure occurring secondary to rapid disease progression during the first course and not considered to be caused by toxicity. None showed clinical or biochemical signs of veno-occlusive disease of the liver. Three died of toxicity (see above), likewise during the first course. Two patients refused therapy after completing one treatment cycle, and one patient with fibrosis of the bone marrow had prolonged thrombocytopenia to the extent that she went off study after receiving only one cycle.

The overall response rate was 26.7%; the median duration of objective response was 5 months (Table 3). Five patients (7%) obtained a complete remission with a median duration of 11 (range, 3–24) months, all were treated with 50% or 75% of the estimated dose. Four were estrogen-receptor-positive and one was estrogen-receptor-negative. A partial remission was achieved by 14 patients (19.7%) and lasted for a median period of 5 (range, 1–13) months; 6 were estrogen-receptor-positive and 8 were estrogen-receptor-negative (Table 4). In all, 18 patients (25%) had stable disease and 20 patients (28%) developed progressive disease.

The response rate recorded for patients previously treated with epirubicin alone was 30.5% (18/59), whereas that noted for patients previously treated with epirubicin plus cisplatin was 8.3% (1/12). This suggests that some degree of cross-resistance existed between

Table 2 WHO hematologic toxicity

	n(%)
Grade 0	–
Grade 1	–
Grade 2	6/71 (9)
Grade 3	17/71 (24)
Grade 4	48/71 (67)

Table 3 Response rate *PD* Progressive disease, *NC* no change, *PR* partial remission, *CR* complete remission)

	n(%)
PD	20 (28.2)
NC	18 (25.2)
PR	14 (19.7)
CR	5 (7)
PR + CR	19 (26.7)
Not evaluable for response	14 (19.7)

Table 4 Characteristics of the 19 responders (*CT* Chemotherapy)

	CR ($n = 5$)	PR ($n = 14$)
Prior adjuvant CT	3	9
Prior CT for advanced disease:		
Epirubicin	4	14
Epirubicin + cisplatin	1	–
Performance status:		
0	–	–
1	2	5
2	3	9
Dominant disease site:		
Soft tissue	1	3
Bone	1	5
Visceral	3	6
Receptor status:		
ER-positive	4	6
ER-negative	1	8

the two alkylating agents CTX and cisplatin. A dose-response effect of the drug was suggested but not demonstrated by the study, and a schedule effect (continuous infusion of the drug) could not be ruled out.

Discussion

The use of high-dose chemotherapy has a sound theoretic basis as substantiated by experimental data and by the superior response rate that several human tumors exhibit for high drug doses as compared with standard doses [19, 20]. With a few exceptions, the major limitation to high-dose treatment is the severity and duration of drug-induced myelosuppression. This holds true not only for authentically myeloablative regimens that require hematopoietic stem-cell reinfusion but also for high-dose treatments that are compatible with a full spontaneous bone marrow reconstitution.

High-dose CTX represents an effective treatment with broad antitumor activity that has been tested in a variety of tumors, including Hodgkin's disease [21], non-Hodgkin's lymphomas [22], small-cell lung cancer [23–25], ovarian carcinoma [26], and breast cancer [27, 28]. In breast cancer, single-agent objective response rates range from 20% to 54% for the most active chemotherapeutic agents [29, 30], with the highest response rates being obtained in previously untreated patients.

The present prospective phase II study evaluated second-line treatment with single-agent CTX every 3 weeks in patients with recurrent breast cancer who had received no cytotoxic treatment for a median of 3 months prior for study entry. The intended dose was 2.5 g/m^2, but virtual doses were on average 25% lower, which yielded a response rate of 26.7%. All patients were previously randomized to treatment with either epirubicin and cisplatin or epirubicin alone. Prior to this, 12 of the 19 responders received a CTX-based regimen (CMF) in an adjuvant setting.

The response rate was equivalent to that obtained with a second-line multi drug regimen. However, the response rate in patients previously treated with epirubicin alone was 30.5% (95% confidence limits, 18.8–45.4%), and in patients previously treated with cisplatin as well the response rate was 8.3% (95% confidence limits, 3.1–20.4%). Thus high-dose CTX given as second-line treatment without cytokine or stem-cell support demonstrates activity in patients with advanced breast cancer who have previously received anthracyclines with or without cisplatin. Our data may be indicative of cross-resistance between CTX and cisplatin. The possibility of survival benefit cannot yet be assessed. An increase in the response rate would be expected to be obtained via dose escalation or dose intensification demanding hemopoietic growth factors, stem-cell support, or both. Despite the seemingly improved results, it has not yet been established whether this therapeutic concept is superior to more conventional therapy.

High-dose, dose-intensive chemotherapy [31] has an excellent initial therapeutic effect in advanced breast cancer, but no study has yet demonstrated an increase in the duration of the remissions or in overall survival beyond that achieved by standard treatment. The role of high-dose and myeloablative antineoplastic therapy can be settled only through randomized trials. In a recent review article, Gurney et al. [32] have discussed this very important issue.

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