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Original Paper

A Phase I Trial of High-dose Paclitaxel, Cyclophosphamide and Mitoxantrone with Autologous Blood Stem Cell Support for the Treatment of Metastatic Breast Cancer

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The aim of this phase I study was to determine the dose limiting toxicity (DLT), maximum tolerated dose (MTD) and efficacy of a new combination of cyclophosphamide (6 g/m^2), mitoxantrone (70 mg/m^2), with dose escalation of paclitaxel (Taxol^R) at a starting dose of 250 mg/m^2 given intravenously over 3 h in a transplantation setting. Patients with metastatic breast cancer and chemosensitive disease were eligible. The autologous blood stem cell re-infusion and subsequent recovery occurred in an out-patient setting. 50 patients were enrolled, but 10 withdrew. 40 completed the entire protocol. At 400 mg/m^2 paclitaxel administered over 3 h, 3 of 6 patients experienced serious adverse events: approximately 20–40 min after completion of infusion, diaphoresis, bradycardia mild hypotension and diarrhoea occurred; 2 patients lost consciousness for a few minutes. An extended infusion schedule delivering 400 mg/m^2 paclitaxel over 6 h rather than 3 h was initiated at this level without patients experiencing this DLT. At the next dose of 450 mg/m^2 paclitaxel over 6 h, the same DLT was seen as at 400 mg/m^2 paclitaxel over 3 h and, therefore, MTD was reached. Time to recovery for the absolute neutrophil count $\geq 0.5\times10^9$/l was 10–19 days (median 12 days); and for platelets $\geq 20\times10^9$/l was 18–20 days (median 11.5 days). 21 patients developed neutropenic fever that required intravenous antibiotics and re-admission; the transfusion frequency for packed red blood cell was 0–5 units (median 2 units) and for platelets, 1–5 encounters (median 2). 13 complete responses, 1 patient with no evidence of disease and 19 partial remissions were documented. The dose of 400 mg/m^2 at an infusion rate of 6 h will be used for the ongoing phase II study to evaluate efficacy and toxicity further. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: breast cancer, metastatic, taxoid, paclitaxel, phase I, combination chemotherapy, ABSC
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INTRODUCTION

BREAST CANCER is the most common malignancy in women, contributing to approximately 25% of malignant tumours and 20% of cancer deaths in female patients [1] in Canada. Once breast cancer becomes metastatic, the disease becomes essentially incurable with a median survival of 15–19 months at the time of indication for chemotherapy [2–5]. The overall response rates for drug regimens is between 20–70% and only a few patients (under 20%) achieve complete remission (CR). In spite of chemotherapy, the majority of patients (80%), have disease progression (PD) within 2 years [2–6]. Most of these patients die within 3 years from documentation of metastasis and there is no report in the literature concerning long-term survival in this subgroup of patients. One way of improving the efficacy of chemotherapy pertains to the dose–effect relationship reported in numerous studies in breast cancer [7, 8]. Evaluation of these data suggests that, for breast cancer, a dose–response effect exists within the range of conventional chemotherapy. Further dose intensification,

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using high-dose chemotherapy, leads to even higher response rates. It has been shown by ourselves and others that high-dose chemotherapy followed by infusion of autologous blood stem cell (ABSC), mobilised by various growth factors, can lead to almost 90% response rates with a CR of approximately 50% [9–20]. It has been shown that, similar to lymphoma, chemosensitive breast tumours tend to have a better overall response rate than chemotherapy resistant tumours [21].

Recently, a new group of chemotherapeutic agents, the taxanes, have been introduced for treatment of malignant diseases [22–26]. Previous clinical phase I/II studies confirmed the activity of one of these agents, paclitaxel (Taxol^R), as an active agent in breast cancer with a favourable toxicity profile [22–26]. Stemmer and colleagues [27] have been able to dose escalate paclitaxel up to 825 mg/m^2 body surface area infused intravenously (i.v.) over 24 h continuously in combination with 5,625 mg/m^2 cyclophosphamide (CTX), 165 mg/m^2 cisplatin (CDDP) and ABSC support [27]. Our group has previously shown that the combination of several drugs active in breast cancer can lead to additive and even synergistic effects *in vitro* [28, 29]. The data clearly show that the combination of paclitaxel and mitoxantrone (MXT) *in vitro* on malignant breast cancer cell lines can show a synergistic effect; and paclitaxel in combination with CTX, an additive effect. Although the extrapolation of *in vitro* data to the clinical situation must be made with caution, it is reasonable to use this drug combination [28, 29] in a clinical trial setting. Therefore, we conducted a phase 1 study, using high-dose CTX (6 g/m^2) and MXT (70 mg/m^2) with ABSC support with dose escalation of paclitaxel. Our goal was to deliver this treatment in a partial out-patient setting, as described previously [30]. This might distinguish this study from many others, but limits the infusion time to less than 8 h.

PATIENTS AND METHODS

Outline of the study

The major end-points of the study were to define the dose limiting toxicity (DLT), the maximum tolerated dose (MTD) and to identify side-effects and toxicities. DLT was defined as grade III or more toxicity according to the WHO scale, except haematotoxicity, alopecia and mucositis. Minor endpoints included response rates after induction chemotherapy and after high-dose chemotherapy and time to haematological recovery. Response rates were defined following the assessment of response to therapy in advanced breast cancer [31]. Progression free survival (PFS) and overall survival (OS) were also recorded. Eligibility criteria included: age 18–55 years, no previous chemotherapy for metastatic disease; adjuvant chemotherapy, if received, had to be completed at least 6 months prior to metastatic disease. Patients needed to have evaluable or measurable disease. Performance status according to Karnofsky was 60% or more. Cardiopulmonary, liver, kidney and haematopoietic functions were normal. The study was approved by the institutional review board. All patients gave written informed consent.

Induction chemotherapy, mobilisation and collection of ABSC

Patients meeting all eligibility criteria received the initial induction chemotherapy consisting of 5-fluorouracil (5-FU) 750 mg/m^2 body surface area, epirubicin (EPI) 100 mg/m^2 body surface area, CTX 750 mg/m^2 body surface area, all delivered on day 1 as an i.v. infusion. Starting on day 4, recombinant human granulocyte colony-stimulating factor (rhG-CSF; Neupogen®, Amgen Canada Inc., Mississauga, Ontario, Canada) at a dose of 10 μg/kg body weight subcutaneously (s.c.), was administered daily for approximately 10–11 days until the total white blood cell count reached more than 2,500 μl. On this day, standard apheresis procedure was performed using a double lumen catheter connected to a Baxter CS3000+. The blood flow was on average 70 ml/min. The processed blood volume was 10 l. The target was to collect at least 5×10^8 mononucleated cells (MNC) per kg/body weight and 2×10^6 CD34+ cells/kg body weight [32]. The procedure was repeated on consecutive days until this target was reached. The ABSCs were cryopreserved in 10% dimethylsulphoxide (DMSO) as previously described by Ho and colleagues [32] and on the day of re-infusion, the cells were thawed, and washed to avoid DMSO-related toxicity [33]. After the first cycle of chemotherapy, the patients received a further two or three cycles of induction chemotherapy consisting of 5-FU 600 mg/m^2 body surface area, EPI 60 mg/m^2 body surface area, CTX 600 mg/m^2 body surface area all administered i.v. The treatment without haematopoietic growth factor support was delivered every 3 weeks if the absolute neutrophil count (ANC) was $\geq 1.5\times10^9$/l and platelets $\geq 100\times10^9$/l. After the three to four cycles of induction chemotherapy, all patients were restaged with a physical examination, imaging studies and blood examination.

High-dose chemotherapy

Only patients who did not progress on induction chemotherapy and did not experience severe toxicity and/or major organ damage proceeded to high-dose chemotherapy. High-dose chemotherapy consisted of CTX 2 g/m^2 i.v.; MXT 23.3 mg/m^2 i.v.; Mesna 300 mg/m^2 i.v. every 8 h. This was delivered on 3 consecutive days for a cumulative dose of CTX 6 g/m^2 and MXT 70 mg/m^2. Appropriate hydration and premedications were administered. On day 4, the paclitaxel dose starting at 250 mg/m^2 body surface area was delivered as a 3 h i.v. infusion. Premedication including oral dexamethasone at 20 mg was given 12 and 6 h prior to infusion as well as H_1 and H_2 antagonist therapy. The 4 days of chemotherapy were administered in the hospital. The patients were usually discharged from hospital for out-patient observation on the day after high-dose chemotherapy [30]. After 48 h of rest, the ABSCs were re-infused and rhG-CSF was administered at the dose of 5 μg/kg body weight s.c. daily until haematological recovery (ANC $\geq 1.5\times10^9$/l) [30, 34].

Group assignments

We planned to treat 5 patients per dose level of paclitaxel. The patients were re-assessed for toxicity, side-effects and response rates 4–6 weeks later and were followed-up every 3 months. Progression of disease, recurrences and survival were recorded. Since the assessment of toxicity was carried out 4–6 weeks after completion of treatments, the availability of data was sometimes delayed, which led to different numbers of patients in some groups.

RESULTS

Patient demographics

Between November 1994 and October 1996, 50 female patients with metastatic (M1) breast cancer were enrolled into the study. 40 patients who did not progress on induction chemotherapy, were eligible for high-dose chemotherapy and

were fully evaluable. The median age was 46 years (range 29–55 years). Before developing metastatic disease, 7 patients were diagnosed with stage I, 22 patients with stage II, 3 patients with stage III breast cancer and 8 patients presented initially M1 disease. The time from diagnosis to PD ranged between 0 (stage IV) and 96 months (median time 20 months). 23 patients were premenopausal and 13 hormone receptor negative. 22 patients received adjuvant chemotherapy and 8 of them received an anthracycline-containing regimen. Only 13 had adjuvant tamoxifen. Table 1 summarises the sites of metastasis and the number of sites involved the patient population. Approximately one-third of patients had three or more sites involved; 16 had lung and eight liver metastasis, representing a poor prognosis population.

Haematological toxicity

Table 2 shows the haematological engraftment for all groups indicating no notable differences between groups, and very short engraftment times of below 2 weeks, comparable to other published studies. In all patients a target of 5×10^8 MNC kg/body weight was reached with at least 2×10^6 CD34+ cells/kg body weight by 1–4 (median 2) apheresis procedures. No differences between groups (data not shown) were observed regarding red blood cell and platelet transfusion frequency, and use of i.v. antibiotics for neutropenic fever: on average, 2 units of PRBC (range 0–5) and 2 bags of single donor platelets (range 1–5) were transfused per patient. 21 patients required i.v. antibiotics for neutropenic fever.

Non-haematological toxicities

Mucositis of grade 3 (according to WHO toxicity grading) was observed only in group 2 (1 of 5 patients), group 3 (3 of 10 patients), group 5 (1 of 6 patients) and group 6 (2 of 9 patients), with no grade 4 mucositis being observed (Table 3). Nausea and vomiting, gastrointestinal, genitourinary, cardiac, and neurological toxicities were moderate and infrequently observed (Table 3). Very few patients experienced bone pain, fatigue, peripheral oedema, redness at the site of rhG-CSF injection, insomnia and occasional reaction to transfusion. Cardiotoxicity, defined as left ventricular ejection fraction dropping below normal values after high-dose chemotherapy, were observed in group 1 (2 of 7 patients), group 3 (2 of 10 patients), group 5 (1 of 6 patients), group 6 (2 of 9 patients), and 1 patient in group 7 (Table 3). 4 of those patients had clinically relevant but reversible symptoms (with 1 exception). This patient had pericardial involvement with metastatic disease (initially without clinical symptoms and with normal LVEF), and had received adjuvant radiotherapy to the left chest as well as adjuvant chemotherapy with a total dose of 720 mg/m^2 EPI. This patient died 5 weeks after transplantation with clinical signs of cardiac failure. No other early or toxic deaths occurred in the study. We observed a thus far novel and unusual DLT: when reaching the dose level of 400 mg/m^2 paclitaxel, 3 of 6 patients experienced diaphoresis, bradycardia, mild hypotension and diarrhoea approximately 20–40 min after completion of infusion; 2 of these 3 patients lost consciousness for a few minutes. Therefore, another 4 patients were treated again at the paclitaxel dose level of 350 mg/m^2, infused over 3 h for a total of 10 patients on this dose level. These side-effects were not observed, so we decided to increase the 350 mg/m^2 paclitaxel infusion time to 6 h; with the extended infusion time, we were able to increase the dose to 400 mg/m^2 paclitaxel in the next 6 patients. At the next level of paclitaxel, 450 mg/m^2 infused

Table 1. *The numbers, in groups according to paclitaxel dose, of patients with different sites of metastasis. Since* 23 *patients had more than one site involved, the total number exceeds the number of evaluable patients treated*

			Sites of metastasis				Number of organs involved		
Group	Paclitaxel dose (mg/m^2) and infusion rate	Number of patients	Bone only ($n=6$)	Liver ($n=8$)	Lung ($n=16$)	Other ($n=21$)	>2 ($n=13$)	2 ($n=11$)	1 ($n=16$)
1	250 (3 h)	7	1	2	5	5	2	3	2
2	300 (3 h)	5	1	1	1	1	0	2	3
3	350 (3 h)	10	2	4	4	6	4	1	5
4	350 (6 h)	2	0	0	1	1	1	0	1
5	400 (3 h)	6	2	0	2	4	0	4	2
6	400 (6 h)	9	0	0	3	3	5	1	3
7	450 (6 h)	1	0	1	0	1	1	0	0

Table 2. *Haematological engraftment for each group. The time (days) from re-infusion of autologous blood stem cells (ABSC) to reach the threshold number of white blood cells (WBC), platelets and absolute neutrophil counts (ANC) is indicated. The numbers represent median values and range*

Group	Paclitaxel dose (mg/m^2) and infusion rate	Number of patients	WBC ≥ 0.5/nl	Platelets ≥ 20 nl	ANC ≥ 0.5/nl
1	250 (3 h)	7	14 (10–15)	15 (8–20)	14 (10–16)
2	300 (3 h)	5	12 (10–12)	12 (9–19)	12 (10–13)
3	350 (3 h)	10	10.5 (10–14)	11.5 (9–17)	11 (10–15)
4	350 (6 h)	2	12 (10–14)	10 (9–11)	13.5 (11–16)
5	400 (3 h)	6	11 (9–19)	10.5 (8–20)	11.5 (10–19)
6	400 (6 h)	9	11 (9–12)	10 (8–18)	12 (10–13)
7	450 (6 h)	1	18	18	19
Total		40	12 (9–19)	11.5 (8–20)	12 (10–19)

Table 3. Non-haematological toxicities; for each group, graded according to WHO scale on toxicity criteria [35]

Group	Paclitaxel dose (mg/m^2) and infusion rate	Number of patients	Mucositis WHO 0–2	Mucositis 3–4	Peripheral neuropathy WHO 0–2	Peripheral neuropathy 3–4	LVEF dropping below normal limit (50%)	Nausea and vomiting WHO 0–2	Nausea and vomiting 3–4	Diarrhoea WHO 0–2	Diarrhoea 3–4	Constipation WHO 0–2	Constipation 3–4	Pulmonary WHO 0–2	Pulmonary 3–4	Renal WHO 0–2	Renal 3–4	Haemorrhagic cystitis
1	250 (3 h)	7	7	0	7	0	2*	7	0	7	0	7	0	7	0	7	0	1
2	300 (3 h)	5	4	1	5	0	0	5	0	5	0	5	0	5	0	4	1	1
3	350 (3 h)	10	7	3	10	0	2	10	0	9	1	10	0	10	0	10	0	0
4	350 (6 h)	2	2	0	2	0	0	2	0	2	0	2	0	2	0	2	0	0
5	400 (3 h)	6	5	1	6	0	1*	6	0	5	1	5	0	6	0	6	0	0
6	400 (6 h)	9	7	2	9	0	2	9	0	9	0	9	0	9	0	9	0	0
7	450 (6 h)	1	1	0	0	1	1*	1	0	1	0	1	0	1	0	1	0	0
Total		40	33	7	39	1	8/40	40	0	38	2	40	0	40	0	40	1	2/40

*clinically relevant. LVEF, left ventricular ejection fraction.

over 6 h, the same complication with loss of consciousness for a few minutes occurred in 1 patient. Therefore, further accrual was terminated and paclitaxel 450 mg/m^2 was defined as MTD.

Response to treatment

Table 4 summarises the response of all 50 patients. 9 were taken off the study because of PD and 1 patient withdrew her consent. 21 patients achieved a partial response (PR) and 9 additional patients a CR with no apparent differences in each group. 40 patients continued treatment with high-dose chemotherapy and ABSC. In Table 5, the response rates of those 40 patients completing the whole protocol are shown: although another 3 patients progressed quickly within 4 weeks of evaluation, 32 of 40 had an objective response with 13 patients reaching a CR. We observed a conversion from PR to CR in 2 patients in group 2, 2 patients in group 3 and 1 patient in group 6, for a total of 5 patients; increasing the number of CRs from 8 to 13 in the high-dose chemotherapy group.

The data on pharmacokinetics will be subsequently published elsewhere.

DISCUSSION

In this study we dose escalated paclitaxel to a dose level of 450 mg/m^2 in combination with high-dose CTX and MXT followed by ABSC transplantation as haematological rescue. At this dose level, which was delivered as a 6 h infusion, we experienced severe DLT as already observed at the 400 mg/m^2 level with a 3 h infusion. Since the regimen was designed to be delivered in an out-patient clinic, further prolongation of the infusion time was not undertaken. In the study published by Stemmer and colleagues 825 mg/m^2 was delivered in an infusion time of 24 h. At this dose level, severe neurotoxicity and mucositis occurred and DLT was reached [27] in combination with CTX and CDDP. In our study, although non-haematological toxicities were generally minor and not life threatening, some important and novel observations were seen: the infusion of paclitaxel at a dose greater than 350 mg/m^2 over 3 h was not possible due to loss of consciousness, hypotension and diaphoresis in a few patients. This has not been reported previously [36]. This observed side-effect might be due to paclitaxel itself, but more likely to the dilution vehicle cremophor EL. Also, the high content of ethyl alcohol in the solution may contribute to, but not cause, the reactions described above. The prolongation of the infusion time from 3 to 6 h could still be given as an out-patient protocol and at the 400 mg/m^2 dose level, entirely abrogated side-effects observed with the 3 h infusion time.

Stemmer and colleagues described mucositis and neurotoxicity as major toxicities [27]. Both of these toxicities were observed in our study but mainly grade I and II according to the WHO criteria. Only a few patients required narcotic analgesics for mucositis or peripheral neuropathy, which mainly presented as pain in the lower limbs.

One of the end-points of our study was to show the feasibility of mobilising and collecting sufficient numbers of haematopoietic progenitor cells for successful transplantation. Since we collected the cells early in the course of the disease, after first induction chemotherapy, the yield was excellent and exceeded our target in most patients after two apheresis procedures. As no bone marrow backup was provided, usually one additional apheresis procedure was performed after reaching our target collection [32].

Although the study was designed as a phase I study, we reported the response rates after induction chemotherapy and after high-dose chemotherapy. At this point, the median PFS of all patients who have chemosensitive disease and obtain the high-dose treatments is more than a year. The response

Table 4. *Response rates after induction therapy just prior to high-dose chemotherapy for each paclitaxel dose*

Group	Paclitaxel dose (mg/m^2) and infusion rate	Number of patients (n = 50)	Progression of disease (n = 9)	Stable disease (n = 11)	Partial response (n = 21)	Complete response/ no evidence of disease (n = 9)
1	250 (3 h)	7	0	1	5	1
2	300 (3 h)	5	0	0	3	2
3	350 (3 h)	10	0	2	7	1
4	350 (6 h)	2	0	0	1	1
5	400 (3 h)	6	0	2	4	0
6	400 (6 h)	9	0	5	1	3
7	450 (6 h)	1	0	1	0	0
	Off study	10	9	0	0	1

Table 5. *Response rates* 4–6 *weeks after high-dose chemotherapy for each group. The patients who were removed from the study prior to high-dose chemotherapy are excluded from response evaluation*

Group	Paclitaxel dose (mg/m^2) and infusion rate	Number of patients	Progression of disease (n = 3)	Stable disease (n = 5)	Partial response (n = 19)	Complete response/ no evidence of disease (n = 13)
1	250 (3 h)	7	1	0	5	1
2	300 (3 h)	5	0	0	1	4
3	350 (3 h)	10	0	2	5	3
4	350 (6 h)	2	0	0	1	1
5	400 (3 h)	6	1	0	5	0
6	400 (6 h)	9	0	3	2	4
7	450 (6 h)	1	1	0	0	0

rates are high and comparable to other high-dose chemotherapy regimens. The Autologous Blood and Marrow Transplantation Registry [21] has described the differences in efficiency between different published protocols as not significant. Considering the fact that taxanes are one of the most active drug groups in breast cancer, it is hoped that better responses, PFS and OS will be possible when used in a high-dose regimen, but this requires confirmation in further phase II studies. Stemmer and colleagues [27], Fields and associates [37], Crown and co-workers [38] and Vermorken and colleagues [39], have used escalating doses of paclitaxel in combination with or without high-dose chemotherapy to improve response rates and outcome in patients with breast cancer and ovarian cancer.

The phase I part of the study as dose escalation is closed to accrual. The study is continuing as a phase II study with the MTD for paclitaxel at 400 mg/m^2 infused over 6 h. A total of 30 patients will be enrolled in order to identify clearly the response rates, the PFS and OS at the 400 mg/m^2 level of paclitaxel. However, only a prospective randomised phase III study will be able to show any true benefit for this patient population.

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