



## Solid tumours

# Phase II study of a multi-course high-dose chemotherapy regimen incorporating cyclophosphamide, thiotepa, and carboplatin in stage IV breast cancer

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### Summary:

The purpose of this study was to determine the feasibility and efficacy of multiple courses of high-dose cyclophosphamide, carboplatin and thiotepa with peripheral blood progenitor cell (PBPC) transplantation in women with advanced breast cancer. Forty-one patients with advanced hormone-refractory breast cancer were enrolled in the study. The treatment started with two courses of 5-fluorouracil 500 mg/m<sup>2</sup>, epirubicin 120 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> (FE<sub>120</sub>C) followed by PBPC harvesting. The high-dose regimen consisted of three subsequent courses of 'tiny' CTC, cyclophosphamide 4000 mg/m<sup>2</sup>, thiotepa 320 mg/m<sup>2</sup> and carboplatin 1060 mg/m<sup>2</sup> (target AUC 13.3 mg/ml/min) (tCTC) divided over 4 consecutive days. The second and third courses were scheduled to begin on day 28 after the previous transplantation. A total of 86 tCTC courses was given to 33 of the 41 enrolled patients. Major toxicities consisted of hemorrhagic cystitis (six patients), prolonged gastro-intestinal toxicity (three patients) and veno-occlusive disease (two patients). There was one therapy-related death (unknown cause). Twenty patients (49%) achieved a complete response, nine (22%) a partial response and three patients stable disease after treatment. The median follow-up of the surviving patients was 43 months (range 25–61). Six patients remain in complete remission beyond 3 years. At 4 years, the progression-free survival (PFS) and overall survival (OS) for the whole patient group were 23 and 30% with a median duration of 12 and 27 months, respectively and for FE<sub>120</sub>C-responsive patients 32 and 36%, respectively with a median duration of 15 and 33 months. In the patient group with a PFS ≥ 18 months all patients had limited disease (metastatic disease in only one or two sites) and fewer patients had bone or liver metastases compared to the overall patient group (33% vs 51%). This report shows that three closely spaced courses of tCTC are feasible, with accept-

able toxicity. Triple tCTC can achieve complete or partial remission in most patients and long-term PFS in a selected subgroup of patients who have limited metastatic disease and are responsive to conventional-dose chemotherapy. *Bone Marrow Transplantation* (2001) 28, 173–180.

**Keywords:** high-dose chemotherapy; metastatic breast cancer; multiple courses; peripheral blood progenitor cell transplantation

Although high-dose chemotherapy with peripheral blood progenitor cell (PBPC) transplantation has been used extensively in the treatment of advanced breast cancer, its ability to achieve long-term disease-free survival is controversial. The evidence that this ability exists is derived from information in the American and European transplant registries<sup>1,2</sup> and also from a large number of small phase II studies (for review see Peters *et al*<sup>3</sup>).

The highest disease-free survival plateaux are found when high-dose chemotherapy is given in first complete remission and when patients have low volume disease.<sup>4–6</sup> At the time of writing, only one randomized study ('the Philadelphia study') has been published<sup>7</sup> and this study did not show any advantage of high-dose alkylating therapy administered as late consolidation.

Since the concept of high-dose chemotherapy for breast cancer is based on solid preclinical evidence, clinical studies that aim to improve its results continue to be worthwhile. The strategy that has been selected by our group is the repeated administration of high-dose cyclophosphamide, thiotepa and carboplatin. A series of three consecutive courses of these agents at the previously reported dose level of cyclophosphamide 6000 mg/m<sup>2</sup>, thiotepa 480 mg/m<sup>2</sup> and carboplatin 1600 mg/m<sup>2</sup>, has been shown to be associated with major toxicities, such as hemorrhagic cystitis, veno-occlusive disease of the liver and hemolytic uremic syndrome, which is considered unacceptable.<sup>8</sup> When the CTC dose is reduced by one-third, however, three subsequent courses with a 4- to 5-week interval appear to be tolerable. Preliminary evidence that this is the case has been reported previously.<sup>9</sup> To document the toxicity pattern and to study the potential of achieving long-term disease-free survival

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with this regimen, we have performed a phase II study in 41 patients with stage IV breast cancer. Our findings suggest that this treatment strategy is feasible and achieves long-term disease-free survival for roughly one-third of patients who are responsive to conventional-dose chemotherapy.

## Patients and methods

### Patient selection

Between September 1994 and January 1998, 41 patients were enrolled in the study. All patients had biopsy-proven stage IV breast cancer. Ages were below 56 years and performance status was excellent (WHO 0 or 1). Patients previously treated with chemotherapy were excluded, except for those who had received non-anthracyclin-based adjuvant therapy more than 1 year before relapse. Patients were eligible if the tumor estrogen-receptor was negative or if they had failed at least one line of hormonal therapy. To avoid the inclusion of patients with massive bone metastases, patients could only be included if there was no bone marrow failure and plain X-rays or bone scans did not show bilateral pelvic lesions. Further criteria for eligibility included adequate bone marrow function (white blood cell count (WBC)  $\geq 4 \times 10^9/l$  and platelet count  $\geq 100 \times 10^9/l$ ), normal liver function tests, a creatinine clearance of at least 80 ml/min, a negative human immunodeficiency virus test, and a negative test for hepatitis B antigen. Written informed consent was obtained from all patients, and the Committee on Medical Ethics of The Netherlands Cancer Institute approved the study.

### Treatment schedule

The treatment started with two courses of FE<sub>120</sub>C (fluorouracil 500 mg/m<sup>2</sup>, epirubicin 120 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup>), all given as an intravenous push on day 1 with a 3-week interval. This is an intensive anthracyclin-based regimen, which we reported previously to be highly efficacious in locally advanced breast cancer.<sup>10</sup> The second FE<sub>120</sub>C course was used for stem cell mobilization. Patients responsive to FE<sub>120</sub>C, including patients with stable disease continued treatment with high-dose chemotherapy. Patients with progressive disease after FE<sub>120</sub>C did not proceed to the high-dose regimen and were taken off protocol treatment. The first course 'tiny CTC' (carboplatin, thiotepa, cyclophosphamide, see below) was started 3 weeks after the last FE<sub>120</sub>C course. The second and third courses were each started 4–5 weeks after the previous one. Resection or irradiation of any residual disease was performed whenever possible after the last course, and sites of previously bulky disease (>5 cm) were irradiated when possible.

### Peripheral blood progenitor cell (PBPC) mobilization and harvest

Peripheral blood progenitor cell mobilization was begun after the second FE<sub>120</sub>C course by the administration of fil-

grastim (300  $\mu$ g subcutaneously, regardless of body weight) from day 2 onwards. Leukocytapheresis started when the white blood cell count exceeded  $3.0 \times 10^9/l$  and the CD34<sup>+</sup> cell count in the peripheral blood was at least 0.5%. All aphereses were performed via 13.5 French double-lumen Hickman catheters or inguinal venous catheters with a continuous flow blood cell separator (Fenwal CS 3000, Baxter Deutschland GmbH, München-Unterschleißheim, Germany). Both the number of CD34<sup>+</sup> cells and the number of granulocyte–macrophage colony-forming units (GM-CFU) were determined in the cell collections. This procedure has been described previously.<sup>11</sup> Based on earlier findings,<sup>12</sup> we considered a graft size of  $3.0 \times 10^6$  CD34<sup>+</sup> cells/kg body weight sufficient for sustained bone marrow recovery and  $1.0 \times 10^6$  CD34<sup>+</sup> cells/kg body weight sufficient for rapid, but possibly transient, granulocyte recovery after high-dose therapy.

### High-dose chemotherapy regimen: 'tiny CTC' (tCTC)

The high-dose regimen tiny CTC was administered as published previously.<sup>8,9</sup> All agents were administered during 4 consecutive days (day -6, -5, -4, and -3). Carboplatin was given intravenously as daily 1-h infusions. The total dose of carboplatin was 1060 mg/m<sup>2</sup> in patients with normal kidney function, but if the creatinine clearance was 110 ml/min or less, the total dose for 4 days was calculated by the formula: dose (mg) =  $13.3 \times (\text{creatinine clearance} + 25)$ . Cyclophosphamide, total dose 4000 mg/m<sup>2</sup>, was given as four daily 1-h infusions, and thiotepa, total dose 320 mg/m<sup>2</sup>, was divided over eight twice-daily  $\frac{1}{2}$ -h infusions. Mesnum (500 mg per dose) was given six times a day for 6 days, starting 1 h before the first cyclophosphamide infusion.

All medication was administered through a central venous catheter inserted in a subclavian vein. Antiemetics were given prophylactically and as needed (usually dexamethasone and granisetron). Prophylactic oral antibiotics were started 3.5 days prior to chemotherapy and included ciprofloxacin and itraconazole or amphotericin B. In addition, all patients received acyclovir orally 400 mg twice daily in the neutropenic period. Roxitromycin was given orally from day 0 onward to prevent gram-positive infections until the neutrophil count exceeded  $0.5 \times 10^9/l$ . Broad spectrum antibiotics were started in cases of a temperature  $>38^\circ\text{C}$ . Peripheral blood progenitor cell (PBPC) reinfusion was performed on day 0. On day 1, filgrastim, (Neupogen, received as a gift from Amgen-Roche, Breda, The Netherlands) 300  $\mu$ g s.c. daily (regardless of body weight) was added to the medication until the WBC count exceeded  $5 \times 10^9/l$ . Irradiated platelet transfusions were given in the event of signs of bleeding or when the platelet count decreased below  $10 \times 10^9/l$ . When hemoglobin levels were below 5.5 mmol/l, leukocyte-free irradiated red blood cells were administered. Whenever possible, patients were discharged from the hospital on the day following PBPC infusion to receive supportive care at home or in a hostel-facility near the hospital.<sup>13</sup>

### Dose adaptations in repeat high-dose chemotherapy courses

Subsequent courses of tCTC were, whenever possible, given at the same dosages as the previous one. In the case of renal dysfunction, the patient was taken off study if the creatinine clearance was below 40 ml/min. If renal function had decreased by 20% from its baseline value, the carboplatin dose was reduced by 50%. In the event of neuropathy grade 3 or significant hearing-loss, the carboplatin dose was reduced by 50%. If mucositis grade 4 had occurred in the previous tCTC, the dosage of all agents was reduced by 25%. Diarrhea grade 4 requiring administration of morphine led to a 25% dose reduction of both cyclophosphamide and thiopeta.

### Results

Forty-one patients were enrolled in the study. Patient characteristics are shown in Table 1. Not all patients received high-dose chemotherapy: eight patients were taken off protocol before tCTC, but remained in the analysis. Seven of these patients were unresponsive to FE<sub>120</sub>C courses and one patient had an estrogen-receptor positive lobular carcinoma. Although she responded to FE<sub>120</sub>C, high-dose chemotherapy did not seem the best treatment

option for this patient. She was taken off protocol as a 'protocol violation' and treated with hormonal therapy.

A total of 86 tCTC courses was administered. Thirty-three patients (80%) received a first course, 30 of these (73%) a second course and 23 patients (56%) a third course too. After the first tCTC, one patient had to stop therapy because of abnormal liver function tests and two patients were taken off study because of lack of response. After the second tCTC, seven patients discontinued therapy because of toxicity: one patient because of sudden unexplained death on day 18 after the second course, three patients because of hemorrhagic cystitis, one patient with asthenia and hematuria, one patient developed veno-occlusive disease and one patient had refractory thrombopenia. The protocol required that the second and third courses of tCTC were started on day 22–29 after the previous PBPC transplantation, while the earliest time point of 22 days was preferred. Following this policy, the median day on which the second and third courses have been started was 29 (range 22–36 and 22–43 days, respectively) after PBPC reinfusion. The second and third courses were delayed beyond day 30 in four and two patients, respectively. Reasons for delay were asthenia (two patients), infection (one patient) or delayed bone marrow recovery (three patients). Dose modifications were applied in three patients, all in the third course. In one patient the dose of all medication was reduced by 25% because of diarrhea, in one patient the carboplatin-dose was reduced by 50% because of ototoxicity. Another patient received no cyclophosphamide in the third course because of hemorrhagic cystitis in the second course. In an additional patient the third course was stopped on day 4 because of an allergic reaction (skin rash, hypotension).

**Table 1** Patient characteristics

Number of patients	41
Median age in years (range)	44 (26–55)
Hormone responsiveness	
ER negative (and PR positive)	28 (2)
ER positive 1st-line HT failure	6 <sup>a</sup>
ER positive 2nd-line HT failure	2
ER unknown, 1st-line HT failure	4
ER unknown	1
Number of sites of disease	
1 site	12
2 sites	19
3 sites	6
4 or more sites	4
Sites of disease	
lymphnodes	23
bone	17
liver	9
lung/pleura	13
skin	4
stomach/intestine	1
local recurrence/chest wall	10
contralateral breast	2
Prior therapy	
radiation therapy	31
adjuvant (after BCS parasternal)	26
advanced disease	5
chemotherapy	10
adjuvant	10

ER = estrogen receptor; PR = progesteron receptor; 1st line HT = first-line hormonal therapy; 2nd line HT = second-line hormonal therapy; BCS = breast conserving surgery.

<sup>a</sup>One patient went off study because she was to have ER/PR positive lobular carcinoma (protocol violation).

### Peripheral blood progenitor cell collection

Peripheral blood cells were collected in 37 patients, following the second FE<sub>120</sub>C course. One patient required a third FE<sub>120</sub>C course for stem cell harvesting.

A median of 33.6 liters (range 10–73) blood per patient was processed in a median of three (range 2–7) apheresis procedures. A median of  $15 \times 10^6$ /kg (range: 5–36) CD34<sup>+</sup> cells and  $186 \times 10^4$ /kg (range: 36–432) CFU-GM per patient were harvested.

**Table 2** Major toxicities of tCTC courses

Toxicity	Number of tCTC courses
Hemorrhagic cystitis	6
Prolonged gastrointestinal toxicity (reversible)	3
Veno-occlusive disease (non-lethal)	2
Allergic reaction to tCTC	2
Radiation pneumonia	2
Symptomatic ototoxicity	1
Unexplained sudden death	1

*Bone marrow reconstitution after multiple tiny CTC*

Neutrophil recovery (defined as neutrophils  $\geq 500 \times 10^6/l$ ) was rapid after the first, second and third cycles. The median value was 10 days for all the three courses. The number of reinfused CD34<sup>+</sup>-cells was not significantly different for the three courses, although the highest number was given after the third cycle. The time to platelet recovery was longer and tended to increase in the second and third cycle (median values 13, 16 and 18 days, respectively). This increase in time to platelet recovery was mainly caused by platelet consumption in patients with veno-occlusive disease or hemorrhagic cystitis. The number of platelet (median of four) and red cell (median of 7 units) transfusions per course was not significantly different over the three courses.

The median inpatient stay after the day of PBPC reinfusion was 2 (range 1–19), 10 (range 1–60) and 4 (range 1–31) days, respectively in the first, second and third cycle. Readmission was necessary in eight, nine and five of the first, second and third cycles, respectively (26% of all 86 tCTC cycles) with a median inpatient stay of 9.5 (range 3–17), 10 (range 3–14) and 19 (range 5–45) days, respectively.

ively. The reason for admission was febrile neutropenia in most cases.

*Organ toxicity of multiple courses tiny CTC*

A total of 86 tCTC courses were given to 33 patients. Twenty-three patients received all three courses, seven patients two courses and three patients only a single course. The major toxicities of tCTC are listed in Table 2.

*Gastro-intestinal toxicity:* Nausea and vomiting varied from occasionally during the days of chemotherapy to grade 3 or 4 gastrointestinal toxicity (according to Common Toxicity Criteria) in seven courses (8%). Prolonged (reversible) gastrointestinal toxicity was seen in three courses. The grade of toxicity tended to increase slightly with the number of courses. Grade 1–2 diarrhea was seen in 79%, 43%, 61% of the first, second and third courses, respectively, and grade 3–4 diarrhea occurred in 6, 13 and 4% of the first, second and third courses, respectively. Mucositis was not very frequent and usually mild. The frequency and severity tended to increase with the number of

**Table 3** Characteristics of patients with a progression-free survival (PFS) longer than 18 months

Patient number (12 patients)	Age (years)	PFS (months)	Response after FE <sub>120</sub> C	Number of sites	Metastatic sites	No of tCTC courses	Radiotherapy after tCTC	Surgery after tCTC	Surv stat
3	50	62+	CR	1	Supraclavicular lymphnodes	3	Chest wall/ parasternal/ McWirther	no	NED
4	39	61+	CR	2	Mastitis, contralateral AL	3	no	Mamma ablation, ALD	NED
14	35	23	PR	2	Liver, pleura	3	no	Metastectomy liver	DO
15	47	29	CR	1	Supraclavicular lymphnodes	3	Right supraclavicular		DO
16	52	48+	PR	2	Local relapse, contralateral axilla	3	no	no	NED
18	32	48+	CR	1	Lung, mediastinum	3	Left upper lobe lung, mediastinum	no	NED
20	49	44+	CR	1	Chest wall relapse	3	Chest wall, lymphnodes	no	NED
21	44	35	PR	2	Lung, bone	3	Humerus thoracic spine, ribs	no	AW
23	49	44+	PR	1	Liver, breast SL, AL	2	Lymphnodes	Metastectomy liver	NED
32	43	32+	PR	2	Local relapse, skin	3	Local radiotherapy and hyperthermia		NED
34	31	30+	NE	1	bone	3	no	no	NED
39	46	25+	CR	1	Supraclavicular lymphnodes	3	Left supraclavicular	no	NED

CR = complete response; PR = partial response; NE = not evaluable; SL = supraclavicular lymphnodes; AL = axillary lymphnodes; ALD = axillary lymphnode dissection; NED = no evidence of disease; AWD = alive with disease; DOD = death of disease.

courses: grade 1–2 toxicity appeared in 6%, 13% and 9% of the first, second and third courses, respectively. Grade 3–4 toxicity only occurred in the third courses (9%). Because of dose adaptations in the second and third courses, the severity of diarrhea, vomiting and mucositis may be underestimated in the later courses. The mean weight loss was 6.3 kg (range 0–15 kg) after three tCTC courses.

**Neurotoxicity and ototoxicity:** Before each tCTC course audiograms were performed. One patient showed a grade 2 ototoxicity after the second tiny CTC course. The audiogram of this patient showed progressive hearing loss of high frequency tones and the dosage of carboplatin was 50% reduced. This patient also had a neurotoxicity grade 1.

Neurotoxicity was seen in five patients and was not more than a grade 1 sensory polyneuropathy, localized in fingers (four patients) and the ulnar nerve (one patient). Three patients mentioned concentration and memory disturbances during the high-dose chemotherapy.

**Cardiopulmonary toxicity:** Minor cardiac toxicity was seen in one of the first courses (3%) and in three (9%) of the second courses. This consisted of bradycardia, possibly associated with the high-dose chemotherapy. In all patients these symptoms were reversible.

Three patients developed respiratory infections requiring antibiotics, all patients during the first course. One patient had a septic shock caused by a bacterial pneumonia, requiring antibiotics and fluid administration. Admission to the intensive care unit was not necessary. All these patients fully completed the three tCTC courses and two of them did not have any pulmonary infection in the next courses.

Two patients developed radiation pneumonia, both 3 months after three courses tiny CTC followed by radiotherapy. Both patients responded rapidly to corticosteroids.

**Liver and renal toxicity:** Most patients had slight liver enzyme elevation during therapy; most of these were reversible and did not worsen in subsequent courses. In two patients the deterioration in liver function was attributable to veno-occlusive (VOD) after the second and third tCTC course, respectively. None of these patients died of VOD. Two other patients with prolonged liver function disorders did not proceed to subsequent courses.

Renal toxicity was minor; only during two courses was a major although reversible elevation of creatinine seen. In none of these patients was the creatinine clearance decreased irreversibly below 50 ml/min.

**Hemorrhagic cystitis:** Reversible hemorrhagic cystitis was seen in six patients varying from mild to moderate. In four patients this complication was one of the reasons for not proceeding to the next course.

**Toxic death:** One patient died suddenly 18 days after stem cell reinfusion, while recovering from the second course of tCTC. The neutrophil count was already normal, but she was still platelet transfusion dependent. Over the preceding days, no abnormalities were noticed. Autopsy was not permitted, so the cause of death remains unclear.

**Other toxicities:** Skin toxicity was frequently seen (in 29% of 86 courses), mostly consisting of mild rashes resolving within 1 or 2 weeks. Only in two courses was a toxicity of grade 3 or more seen. One patient developed hand-foot syndrome. All skin lesions resolved, sometimes with irregular skin pigmentation.

Fever was seen with many courses. In the first, second and third courses, a temperature  $>39^{\circ}\text{C}$  was seen in 48, 70 and 52%, respectively. The fever period was mostly brief with a median duration in all three courses of about 2–2.5 days.

An allergic reaction to tCTC therapy was seen in two patients, both in the third course. In one patient the course was discontinued for this reason. In the other patient only a skin reaction consisting of prurigo and rash was seen.

Unexpectedly irreversible alopecia was seen in four patients (follow-up time 25–52 months). In two of these patients some hair growth occurred later, but it was patchy and never became normal.

**Second tumors:** In one patient melanoma Clarke IV was diagnosed and treated by surgery. No other second tumors have been diagnosed to date.

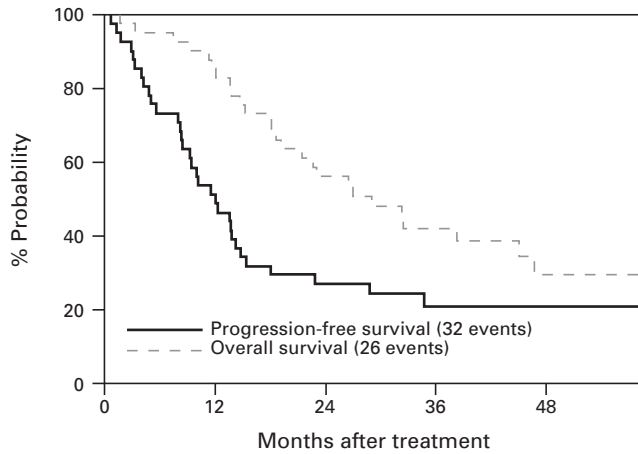
#### *Response to chemotherapy*

A total of 25 (61%) patients achieved an objective remission (17 partial (PR) and eight complete (CR) responses after FEC courses). Twenty-four of these patients and nine of 11 patients with stable disease, minimal response or no evaluable disease proceeded to high-dose chemotherapy. Twenty patients (49% of all patients) had a complete and nine (22%) a partial remission after high-dose chemotherapy. Twelve of the 17 (70%) patients with a partial remission after FE<sub>120</sub>C courses converted to a complete response after tCTC courses. One patient had a clinical CR and underwent salvage mastectomy. The pathological specimen showed two residual micrometastases. Two patients with a PR after tCTC achieved CR after partial liver resection. Pathologic examination of the resected liver tissue showed only necrosis in one of these patients, but in the other patient viable tumor was seen.

#### *Survival*

At the time of this analysis, the median follow-up duration in surviving patients was 43 months (range 25–61). Fifteen (37%) of the 41 patients were still alive, nine (22%) with no evidence of disease (survival duration 25–62+ months) and six (15%) patients were alive with disease (survival duration 26–62+ months).

Overall survival (OS) at 3 and 4 years after treatment was 40% and 30%, respectively, for the whole patient group. Progression-free survival 3 years and 4 years after treatment was 23% for the whole group (Figure 1). Median overall survival was 27 months and median progression-free survival was 12 months for the whole group. OS and PFS for the patient group treated with high-dose chemotherapy were not different from the overall patient group: 29 and 28%, with a median duration of 28 and 11 months, respectively. As expected, the group of patients with a com-



**Figure 1** Overall survival of all 41 patients enrolled in the study. The median survival duration was 27 months. The thin lines indicate the Greenwood (95%) confidence interval (CI).

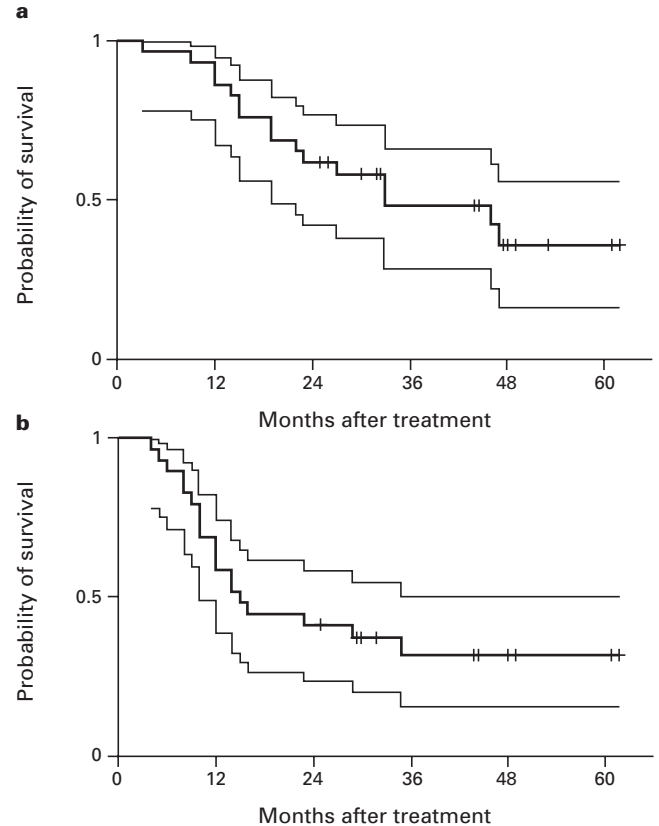
plete or partial response to FE<sub>120</sub>C chemotherapy had a better OS and PFS than did the chemotherapy-refractory patients. If the analysis is limited to the (favorable) subgroup of these 29 patients who had some evidence of tumor regression ( $\geq 25\%$ ) after two courses of FE<sub>120</sub>C (including two patients with non-evaluable disease), nine of these patients (31%) are still alive without disease 25–61 months after start of treatment. The survival-curves for FE<sub>120</sub>C-responders show a PFS and OS of 32 and 36%, respectively at 4 years and a median PFS and OS duration of 15 and 33 months, respectively (Figure 2).

Some of characteristics of the patients with a progression-free survival longer than 18 months ('long PFS-group') are shown in Table 3. Although the groups are small, these data strongly suggest that in this 'long PFS-group' more patients have limited disease (metastatic disease in only one or two sites). In this group all patients had only one or two metastatic sites, but in the patient group with a PFS shorter than 18 months only 65% had limited disease. In addition, most patients in the 'long PFS group' had soft tissue metastases (skin, lymph nodes, local recurrences) and less bone or liver involvement: bone and liver metastases were seen in 33% in the 'long PFS-group' vs 51% in the overall patient group. In this study, age did not differ between the groups with a PFS longer or shorter than 18 months.

## Discussion

The ultimate goal of repeated high-dose chemotherapy in stage IV breast cancer is to achieve long-term survival for at least a subgroup of patients. This hope is not unrealistic since a large number of phase II studies and also data from both the American and European bone marrow registries suggest that a small proportion of patients survives free of disease without further treatment.<sup>1–3</sup> It is the objective of our triple tCTC regimen to increase the level of this 'tail of the survival-curve'.

Several authors have reported on prognostic factors predicting survival after high-dose therapy.<sup>4–6,14,15</sup> Most stud-



**Figure 2** (a) Overall survival in the 29 FE<sub>120</sub>C-responsive patients. The median OS was 36% with a median duration of 33 months. (b) Progression-free survival in the 29 FE<sub>120</sub>C-responsive patients. The median PFS was 32% with a median duration of 15 months. The thin lines indicate the Greenwood (95%) confidence interval (CI).

ies agree that the patients most likely to benefit from intensive chemotherapy are patients with limited metastatic disease, who are in good clinical condition and who respond to conventional-dose chemotherapy. The findings in our phase II study are entirely consistent with this concept. Some authors have found that tumors with a positive estrogen receptor do better than tumors with a negative one, but this is controversial.<sup>6,16,17</sup> We have selected our patients for either estrogen receptor negativity or for failure to respond to endocrine treatment. We believe that high-dose chemotherapy continues to be an experimental treatment modality and should be restricted to patients in whom the likelihood of a satisfactory and durable response with hormonal agents is small.

The design of high-dose chemotherapy regimens for advanced breast cancer continues to be a subject of debate. Several investigators have argued that high-dose chemotherapy should be given up-front, without conventional-dose induction chemotherapy.<sup>18,19</sup> There are no clinical studies reported thus far, which convincingly support this hypothesis. There are certain mathematical models that support the high-dose chemotherapy up-front concept,<sup>19,20</sup> but it is at present unclear whether mathematical models have any predictive value. In contrast, high-dose chemotherapy as late intensification has been shown to be effective in other tumors, such as non-Hodgkin's lymphoma<sup>21</sup> and con-

ventional chemotherapy offers the additional benefit that it helps to identify a patient population that is more likely to derive long-term benefit.<sup>22</sup>

High-dose chemotherapy can induce a long-term survival in a subgroup of patients, but the question remains as to whether this subgroup is larger than that which achieves long-term disease-free survival after conventional-dose chemotherapy. The only randomized study addressing this is the recently published study of Stadtmauer *et al* (Philadelphia study).<sup>7</sup> In this study all patients received between four and six cycles of standard combination chemotherapy. Patients with a complete or partial response were randomly assigned to receive either a single course of high-dose carboplatin, thiotepa, and cyclophosphamide plus autologous hematopoietic stem cell transplantation or 24 cycles of conventional chemotherapy (cyclophosphamide, 5-fluorouracil, methotrexate). Disappointingly, this study does not show a difference in disease-free survival between the patients in the standard-dose arm and the high-dose arm. The standard-arm in this study contains a relatively high cumulative dose of cyclophosphamide: a median of eight additional courses of CMF (cumulative cyclophosphamide dose 11.2 g/m<sup>2</sup>) was given to the patients randomized to the conventional arm of the study. This is almost double the dose of cyclophosphamide in the CTCb regimen. If it is true that certain tumors require either a high-dose cumulative dose of chemotherapy or a long period of treatment, then these tumors were more effectively treated in the conventional arm. However, this comment certainly does not invalidate the results of the 'Philadelphia study'.

Another matter of debate is whether or not repeated high-dose chemotherapy can best be given as high-dose alternating chemotherapy, in which several different agents are used sequentially at their maximum dose,<sup>23,24</sup> or if repeated administration of the same high-dose regimen in a tight time-frame would be preferable. We have advocated the latter approach, mainly because alternating chemotherapy has not shown any clinical advantage in the conventional-dose setting.<sup>25-27</sup> It is difficult to see why different laws would govern the administration of high-dose chemotherapy than govern conventional-dose chemotherapy. A drawback of repeating the same high-dose regimen, however, is the threat of severe end-organ toxicity. The present study shows that such toxicity is acceptable and manageable, but it requires a decrease in the chemotherapy dose below the dose that can be tolerated when only a single course is given. Since we are uninformed about the shape of the dose-response curve in advanced breast cancer (this curve may be different for each individual tumor)<sup>28</sup> we do not know at this point if this is a significant drawback.

Results of the intensive treatment regimen are encouraging and it might be possible to increase 'tail of the survival curve', especially in the FE<sub>120</sub>C responsive patients. However, since the patient group was small and highly selected (good performance status, only 25% of patients previously treated with chemotherapy, young age, no massive bone metastases), no firm conclusions can be drawn.

Sixty percent (20 of the 33) patients receiving at least one course of high-dose chemotherapy achieved a complete response. More importantly, long-term disease-free survival

(here defined as disease-free survival beyond 3 years) was 21% for the whole patient group and 32% for patients responsive to conventional-dose chemotherapy. Moreover, in 10 of the 12 patients with a PFS beyond 3 years it was possible to complete high-dose treatment with local radiotherapy or surgery on residual disease. This could have contributed to an increase in PFS.

Most patients with a PFS beyond 3 years had soft tissue metastases (skin, lymph nodes, local recurrences) and less bone or liver involvement: (51% in the overall patient group vs 33% in the patients with a PFS >3 years). This is not unexpected, as limited disease, soft tissue involvement and response to chemotherapy are also favorable factors with conventional chemotherapy.

Even if the survival curves represent an improvement in what could be achieved with conventional-dose chemotherapy,<sup>29</sup> it is clear that many patients in complete remission eventually relapse. It is apparently possible to induce a state of minimal residual disease in the majority of patients when high-dose chemotherapy is applied.

These considerations leave us with two broad strategies to further improve the results of high-dose chemotherapy in hormone refractory patients with advanced breast cancer. The first is better selection of tumors likely to respond to high doses of alkylating agents. This is at present impossible, but it may well be that certain genetic characteristics of tumors will be shown to be predictive in the near future. We hope that the simultaneous measurement of expression of many genes that has recently become possible by microarray analysis will help to select these tumors.<sup>30,31</sup> A second approach is to attempt to eradicate or at least control micrometastatic disease by immunotherapy, anti-angiogenesis agents or by other non-myelosuppressive treatment with non-cross-resistant drugs. Recent reports have suggested, for example, that paclitaxel can be used safely in the post-transplant setting without profound myelosuppression.<sup>32</sup>

Repeated high-dose chemotherapy continues to be a viable, although experimental option in the treatment of patients with limited stage IV breast cancer, who respond to conventional chemotherapy.

Since treatment strategies and supportive care technology continue to evolve rapidly, it may be too early to compare the present treatment with conventional chemotherapy.

Further studies may teach us which patients will derive most benefit from repeated high-dose therapy. Additional innovative strategies are warranted to maintain complete remission.

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