Randomised trial of high-dose chemotherapy and haemopoietic progenitor-cell support in operable breast cancer with extensive axillary lymph-node involvement

Sjoerd Rodenhuis, Dick J Richel, Elsken van der Wall, Jan H Schornagel, Joke W Baars, Caro C E Koning, Johannes L Peterse, Jacques H Borger, Willem J Nooijen, Roel Bakx, Otilia Dalesio, Emiel Rutgers

Summary

Background Uncontrolled studies suggest that high-dose chemotherapy is beneficial in patients with breast cancer and multiple metastases to the axillary lymph nodes. Many physicians accept this treatment as standard care. We aimed to assess adjuvant high-dose chemotherapy in breast cancer in a phase II randomised trial.

Methods 97 women aged younger than 60 years, who had breast cancer with extensive axillary-node metastases (confirmed by a tumour-positive infraclavicular lymph-node biopsy), received three courses of up-front chemotherapy ($FE_{120}C$). This regimen consisted of cyclophosphamide 500 mg/m^2, epirubicin 120 mg/m^2, and 5-fluorouracil 500 mg/m^2 once weekly for 3 weeks. After surgery, stable patients or those who responded to chemotherapy were randomly assigned conventional therapy (fourth course of $FE_{120}C$, followed by radiation therapy and 2 years of tamoxifen [40 patients]) or high-dose therapy (identical treatment but an additional high-dose regimen and peripheral-blood progenitor-cell [PBPC] support after the fourth $FE_{120}C$ course [41 patients]). This high-dose regimen comprised cyclophosphamide 6 g/m^2, thiotepa 480 mg/m^2, and carboplatin 1600 mg/m^2. The primary endpoint was overall and disease-free survival. All analyses were by intention to treat.

Findings No patients died from toxic effects of chemotherapy. With a median follow-up of 49 (range 21–76) months, the 4-year overall and relapse-free survivals for all 97 patients were 75% and 54%, respectively. There was no significant difference in survival between the patients on conventional therapy and those on high-dose therapy.

Interpretation High-dose therapy is associated with substantial cost and acute toxic effects, but also has potentially irreversible long-term effects. Until the benefit of this therapy is substantiated by large-scale phase III trials, high-dose chemotherapy should not be used in the adjuvant treatment of breast cancer, apart from in randomised studies.

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Departments of Medical Oncology (Prof S Rodenhuis MD, D J Richel MD, E van der Wall MD, J H Schornagel MD, J W Baars MD), **Radiation Therapy** (C C E Koning MD, J H Borger MD), **Clinical Pathology** (J L Peterse MD), **Clinical Chemistry** (W J Nooijen PhD), **Biometrics Department** (R Bakx MSc, O Dalesio MSc), **and Surgical Oncology** (E Rugters MD), **Netherlands Cancer Institute, Amsterdam, Netherlands**

Correspondence to: Dr Sjoerd Rodenhuis, Department of Medical Oncology, Netherlands Cancer Institute, 1066 CX Amsterdam, Netherlands (e-mail: sroden@nki.nl)

Introduction

High-dose chemotherapy with haemopoietic-progenitor-cell support is widely used in high-risk breast cancer.[1] This therapy, however, is expensive, and has a moderate risk of morbidity and mortality. Moreover, the superiority of high-dose chemotherapy over conventional chemotherapy has not been established by randomised trials. Nevertheless, many oncologists and patients are so convinced of the benefits of high-dose therapy that they are unwilling to take part in randomised trials.[2,3]

The belief that high-dose therapy is beneficial stems from laboratory findings that showed a log-linear dose-response relation for tumour cell-lines exposed to alkylating agents.[4,5] Small uncontrolled studies also suggested that breast-cancer patients with extensive axillary lymph-node involvement who received high-dose therapy have better progression-free and overall survival than historical controls. Peters and colleagues' 1993 study[6] is the most influential. 85 patients with breast cancer who had ten or more tumour-positive axillary lymph nodes received four courses of cyclophosphamide, doxorubicin, and 5-fluorouracil, which was followed by high-dose therapy with cisplatin, cyclophosphamide, and carmustine (CPB). At the median follow-up of 3·3 years, actuarial event-free survival was 72% and overall survival was 77%. There were no relapses after 28 months of follow-up.[6] The outcome of patients after CPB therapy seemed superior to that in historical controls who had received conventional chemotherapy for similar tumours. Randomised studies were started in response to these findings.

2 years before the publication of Peters and co-workers' report,[6] we began a randomised study at the Netherlands Cancer Institute. We aimed to integrate high-dose therapy and the new technology of peripheral-blood progenitor-cell (PBPC) support into a treatment strategy that could be assessed in a multicentre setting in the Netherlands. Our study is the first randomised trial of high-dose therapy in the adjuvant treatment of high-risk breast cancer to report data on relapse-free and overall survival. Various large, randomised phase III studies are underway in the USA and in Europe, but are not expected to report preliminary survival data until the end of the century.[7,8] We did not set out to settle the question of whether or not high-dose therapy should be offered to young women with high-risk breast cancer, although we hope to contribute data for the meta-analysis that should eventually provide a reliable answer. Our primary goal was to develop a practical approach that could be used in a large-scale multicentre study of this treatment question; such a trial is currently underway.

Methods

Patients

The study was designed for women younger than 60 years who had epithelial breast cancer with extensive involvement of level III axillary lymph nodes, which we confirmed by a tumour-positive axillary apex node on infraclavicular lymph-node biopsy.[9,10] Involvement of level III lymph nodes is usually associated with extensive axillary-node involvement[11] and has a poor prognosis.[12] Apart from the axilla, the tumour was required to be operable according to classic Haagensen criteria.[13] Women who had had a tumorectomy from the breast to obtain a biopsy sample were eligible, provided that no axillary dissection had been done. The absence of distant metastases was confirmed by physical examination, a chest radiograph, a liver ultrasound examination, and a radionuclide bone scan, all of which were required to be normal. Computed-tomography scans of the brain and liver and bone-marrow examinations were not done. Eligible patients had to have normal bone marrow, renal, and hepatic functions, with a WHO performance status of 0 or 1.

Written informed consent was obtained from all patients before enrolment in the study, according to institutional guidelines. Patients were again asked for their permission to take part after up-front chemotherapy and surgery and before randomisation. The protocol was approved by the Netherlands Cancer Institute's protocol review committee and the committee for medical ethics of the Netherlands Cancer Institute.

Study design

The study was designed as a single-institution phase II study. We aimed to assess the feasibility and efficacy of three courses of up-front anthracycline-based chemotherapy ($FE_{120}C$) with a high dose of epirubicin followed by surgery and a fourth course of chemotherapy in women with high-risk breast cancer. $FE_{120}C$ therapy was followed by radiation therapy and hormonal treatment. After surgery, all patients who were stable or had responded to chemotherapy were randomly allocated a further course of $FE_{120}C$ followed by radiation therapy plus 2 years of tamoxifen (conventional treatment) or identical treatment with high-dose therapy and autologous peripheral-blood progenitor cell (PBPC) support before the radiation therapy.

Treatment

Patients randomised to conventional treatment received three courses of $FE_{120}C$. Courses were given once every 3 weeks and consisted of intravenous push injections of 5-fluorouracil 500 mg/m^2, epirubicin 120 mg/m^2, and cyclophosphamide 500 mg/m^2. We have previously published the feasibility of this high-dose anthracyclin-based regimen in young patients with primary breast cancer who have had no previous treatment.[14] After each course, the patients' response was assessed clinically. We intended to withdraw patients from the study who had progression during induction chemotherapy. Since no patient had progression, however, this rule was not applied. All patients underwent definitive surgery after the third course that included an axillary lymph-node dissection. The type of surgery was predetermined before chemotherapy. Breast-conserving therapy was applied only when this approach was deemed appropriate by the surgeon before up-front chemotherapy. In all other cases, a modified radical mastectomy was done. Thus, the extent of the surgery was not adjusted for reduction of tumour volume after chemotherapy. Patients who were judged to have chemosensitive disease (based on clinical response or on the findings at microscopic examination of the resection specimen) received a fourth $FE_{120}C$ course, followed by radiation therapy to the chest wall, the parasternal region, the axilla, and the infraclavicular and supraclavicular regions. The specific radiation doses and volumes have been described elsewhere.[15] The treatment was completed by tamoxifen 40 mg daily for 2 years.

Patients assigned the high-dose therapy received identical conventional therapy, except that high-dose therapy with PBPC

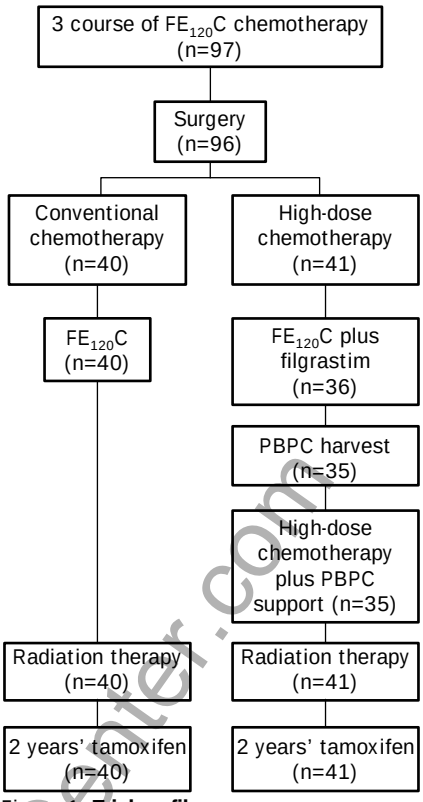

Figure 1: **Trial profile**
PBSC=peripheral-blood progenitor cell.

support was given after the fourth $FE_{120}C$ course. The fourth $FE_{120}C$ course was used to mobilise PBPCs; we used granulocyte colony-stimulating factor (filgrastim) in a 300 μg daily subcutaneous dose, irrespective of bodyweight. PBPCs were harvested by leucocytaphereses that began when the white-blood-cell count exceeded $3{\cdot}0\times10^9$/L and continued until at least $3{\cdot}0\times10^6$ CD34 cells per kg bodyweight had been collected. We have described details of the procedures elsewhere.[16,17] High-dose chemotherapy started 21 days after the fourth $FE_{120}C$ course. The high-dose regimen consisted of cyclophosphamide 6 g/m^2, thiotepa 480 mg/m^2, and carboplatin 1600 mg/m^2, which was divided over 4 days.[18] After 2 days of rest, the PBPC reinfusion took place.

Antiemetics were used prophylactically and then as needed by each patient, and usually included dexamethasone, ondansetron, or granisetron. All patients received prophylactic antibiotics, including oral ciprofloxacin and amphotericin B for selective bowel decontamination. Benzyl penicillin (1 million U four times daily) and amphotericin B (0·25 mg/kg daily) were given prophylactically from the day of progenitor-cell reinfusion (day 0) and were discontinued when the neutrophil cell count exceeded $0{\cdot}5\times10^9$/L. Patients who tested positive for antibodies to herpes simplex virus received prophylactic oral aciclovir 400 mg twice daily. Irradiated platelet transfusions were administered to maintain platelet counts of at least 10×10^9/L, and irradiated leucocyte-free red blood cells were given to maintain haemoglobin concentrations at or above 5·5 mmol/L. The patients stayed in private hospital rooms between day 0 and the end of absolute neutropenia, but no other reverse isolation measures were used. Filgrastim 300 μg was administered as a daily subcutaneous injection, irrespective of bodyweight, from day 1 until the white-blood-cell count exceeded $5{\cdot}0\times10^9$/L.

Assessment of patients' response

We used standard criteria to assess the effects of the three up-front chemotherapy courses. Serial mammographies were not done routinely in all patients, and were frequently difficult to interpret because of dense glandular tissue, and were not, therefore, used for response evaluation.

	$FE_{120}C$ chemotherapy		
	First course (97 patients)	Second course (96 patients)*	Third course (96 patients)*
Delays	0	3	9
Dose reductions	0	1	2
Nausea and vomiting			
Grade III	3	3	1
Grade IV	1	1	0
Mucositis			
Grade III	2	2	0
Grade IV	0	0	0
Neutropenic fever	9	0	3

*One patient refused treatment after first course.

Table 1: **Feasibility and toxic effects of up-front $FE_{120}C$ chemotherapy (289 courses) in all patients before randomisation**

We defined clinical complete remission as the disappearance of all palpable tumour in the breast and in the axilla, as assessed by a surgeon and a medical oncologist. A clinical partial remission was defined as a decrease of at least 50% of the sums of all perpendicular diameters of palpable lesions in breast and axilla. We defined progressive diseases as an increase of 25% of all palpable tumour or the appearance of any lesion not present at the start of treatment. Stable disease was a decrease in size of less than 50% or an increase of less than 25%.

All resection specimens were reviewed for response to chemotherapy by one of us (JLP). The absence of tumour cells, both in the breast and in the axilla, was regarded as a pathological complete remission. The absence of infiltrating carcinoma but presence of carcinoma-in-situ combined with negative axillary lymph nodes was classified as a complete remission with carcinoma-in-situ. Signs of the effects of chemotherapy, such as extensive fibrosis with only small nests of tumour cells or extensive necrosis but remaining areas with vital tumour, were classified as no complete remission.

All patients with a clinically complete or partial response or with a pathologically complete response were offered randomisation. Patients with stable disease were initially offered randomisation when there was a minimal response according to the physician, evidence of response to chemotherapy in the resection specimen, or a subjective response. Because of the poor reproducibility of these evaluations, however, it was later decided to offer randomisation to all patients without progression.

Statistical analysis

The study was designed to ensure a power of 80% for the detection of a 30% increase in progression-free survival at 4 years (30–60%) in the high-dose therapy group compared with the conventional chemotherapy group alone (1-tailed test, α=0·05). We calculated that 70 patients (35 patients in each group) would need to be randomised and followed up until 38 events were observed. This report was prepared after the 38th event.

Treatment assignment was done by the minimisation technique with stratification for clinically complete response (yes or no) and postmenopausal status (yes or no). The primary endpoints were overall and relapse-free survival.

The treatment comparisons were done by intention to treat. Survival curves were constructed by the Kaplan-Meier method and compared by the log-rank test. We used Cox's model to analyse the factors predictive of progression or death and adjust the comparison of treatments for the patients' baseline characteristics.

For the univariate and multivariate analyses, possible prognostic factors for relapse-free and overall survival from the start of treatment were examined. For each variable, Kaplan-Meier curves and the graph of the log (-log survival function) versus log (time) were plotted and checked for proportionality of hazards. For these plots, continuous variables were divided by the median as cut-off points. For progression-free survival and overall survival, each variable was screened univariately by means of Cox's proportional hazards model. Discrete variables with more than two categories were analysed by means of the catgories or by indicator variables (clinical T stage). A forward stepwise procedure was planned with those variables found to be significant in the screening. No variable passed this step. Factors studied were age, clinical T stage, histology, and a series of tumour characteristics, including nuclear grade, oestrogen and progesterone receptors, and neu and p53 expression.

We constructed another set of models to adjust the treatment groups for the possible effect of prognostic factors. In addition to clinical T stage, we examined clinical and pathological response to chemotherapy and high-dose treatment (both actual treatment and intention to treat). Survival and time to progression by treatment group were compared by the log-rank test, with stratification by clinical T stage.

Clinical tumour response	n	Microscopic examination of breast and axilla*	No breast tumour		Residual	
			Axilla negative	Axilla positive	Axilla negative	Axilla positive
Complete remission	15	15	2	6	0	7
Partial remission	57	50	1	2	1	46
No complete remission	17	16	0	0	0	16
Not evaluable	7	2	0	1	0	1

*Microscopic assessment of primary tumour after chemotherapy was not possible in patients who had undergone a tumorectomy at the time of diagnosis.

Table 2: **Clinical and pathological responses to up-front $FE_{120}C$ chemotherapy**

Results

Between April 5, 1991, and Dec 19, 1995, 97 patients were enrolled in the study (figure 1). We were able to assess overall survival and disease-free survival, but eight patients were not clinically evaluable for response to up-front chemotherapy because their tumour had been excised at the time of the infraclavicular biopsy and no palpable lesions remained. These eight patients were included in all analyses, apart from the analysis of response to chemotherapy. Six further patients had undergone excisions of their primary breast tumours, but had palpable axillary lymph nodes that allowed clinical assessment of response. 81 patients were randomised after surgery.

Up-front chemotherapy

The three courses of $FE_{120}C$ were well-tolerated; 96 patients received all three courses, and 94% of the second and third courses of $FE_{120}C$ were given at the planned time, 21 days after the previous course (table 1). Despite the high dose of epirubicin, dose reductions were exceptional and were applied in less than 2% of second and third courses. The toxic effects of the three courses were generally mild and consisted of nausea and vomiting (which was usually well controlled with antimetics), alopecia (in all patients), fatigue (most patients), mucositis (28% as % of chemotherapy courses), phlebitis (4%), and diarrhoea (4%). Neutropenia was common and neutropenic fever occurred after 12 (4%) of the courses. Some of the toxic effects are shown in table 1.

Chemotherapy was effective in inducing clinical and pathological responses. The objective response rates are shown in table 2. There was no complete agreement between the clinical and pathological evaluations of the effects of therapy. In the 89 patients who had evaluable tumours, the clinical assessment was done by physical examination of the resection specimens of the breast and

Index of recovery	Median (range)
Neutrophil count >0·5×10⁹/L	10 (8–28)
Platelet transfusion independence (days)*	13 (7–23)
Fever >38°C (days)	5 (0–15)
Day of discharge†	13 (13–30)
Number of red-blood-cell transfusions (units)	4 (2–12)
Number of platelet transfusions (occasions)	3 (1–21)

All data are median (range). *Platelets≥20×10⁹/L without platelet transfusions. †Day 0=day of reinfusion; chemotherapy began 6 days before reinfusion.

Table 3: **Haemopoietic recovery after PBPC reinfusion in 35 patients on high-dose chemotherapy**

the axilla after chemotherapy. In 83 patients, the resection specimens of both the primary tumour and the axilla were available for microscopic examination.

Surgery

81 patients underwent a planned modified radical mastectomy. 16 patients underwent breast-conserving surgery, which included an axillary lymph-node dissection. There were no major complications from surgery.

Randomisation

16 of the 97 patients were not randomised after the three courses of up-front chemotherapy. 11 patients refused to take part because they were reluctant to undergo high-dose therapy. In five patients, unresponsiveness to $FE_{120}C$ was the main reason not to continue protocol treatment.

Mobilisation and harvest of PBPCs

The mobilisaton and harvest of PBPCs was successful in all but one patient, who was later found to have a myelodysplastic syndrome (refractory anaemia) without chromosomal abnormalities. This patient is not included in the analysis. The findings in a subgroup of 40 patients have been published previously.[14] Briefly, we found that CD34 cell counts had a similar accuracy in prediction of haemopoietic recovery as the colony-forming-unit granulocyte-macrophage (CFU-GM) colony assays. Consequently, the CD34 cell count was adopted as the only routine indicator of graft size. Median values for graft sizes and the number of leucocytophareses in the 40 patients were: 2 (range 1–4) aphereses per patient; 350×10^8 (155–1383) mononuclear cells; $8{\cdot}4\times10^6$/kg (0·6–26·6) CD34 cells; and $38{\cdot}4\times10^4$/kg (1·9–205) CFU-GM. The first three patients in the study also received autologous bone-marrow grafts.

High-dose chemotherapy and PBPC support

81 patients were randomised: 40 to conventional-dose therapy and 41 to high-dose therapy with PBPC support. Only 35 of the 41 patients received high-dose therapy: five refused high-dose therapy despite having previously agreed with this policy. All 35 patients had conventional chemotherapy instead. A sixth patient did not undergo high-dose therapy because she did not mobilise PBPCs.

The high-dose therapy was moderately well tolerated. There were no toxic deaths, but there were substantial, although reversible, toxic effects, which we have previously described.[17] 30 patients had some degree of mucositis, which was grade III in seven patients and grade IV in one patient. Other common toxic effects included fatigue and diarhoea. Reversible renal failure (defined as a doubling of the initial serum concentration of creatinine) occurred in three patients. No patients had haemorrhagic cystitis, veno-occlusive disease of the liver, or haemolytic uraemic syndrome.

Haemopoietic recovery was rapid in all patients. 31 (90%) patients were discharged from the hospital on or before day 18 after the reinfusion of PBPCs. Table 3shows some pertinent data on recovery. During high-dose therapy all premenopausal women became menopausal and remained menopausal during follow-up.

Radiation therapy, tamoxifen, and follow-up

Radiation therapy was well-tolerated after both conventional and high-dose therapy. We have already reported findings in a subgroup of patients.[15] Briefly, bone-marrow suppression was slightly more pronounced during radiation therapy after high-dose therapy than after conventional therapy, but did not affect the scheduled radiation therapy. Four patients on high-dose chemotherapy developed radiation pneumonitis that required the administration of corticosteroids, between 3 and 12 weeks after the completion of radiation therapy; all four responded rapidly to treatment with prednisolone.

	High-dose therapy (n=41)	Conventional therapy (n=40)
Mean (range) age in years	45 (25–57)	48 (28–59)
Pre-menopausal	31	33
Surgery		
Mastectomy	34	33
Breast-conserving treatment	7	7
Oestrogen-receptor status		
Positive	7	6
Borderline	2	1
Negative	11	10
Unknown	21	23
Progesterone-receptor status		
Positive	5	3
Borderline	5	1
Negative	10	13
Unknown	21	23
At diagnosis		
T1	1	3
T2	11	13
T3	21	16
T4	4	4
Tx	4	4
N0	0	1
N1	36	32
N2	4	7
After chemotherapy at surgery		
pT0	3	5
pT1	8	12
pT2	18	14
pT3	4	7
pT4	1	0
Not evaluable	7	2
pN0	2	1
pN1	38	38
pN2	0	1
pNx	1	0
p53 status		
Positive	10	11
Indeterminate	4	5
Negative	22	21
Neu status		
Positive	6	7
Indeterminate	1	0
Negative	29	30

For hormone receptors and p53, tumours were judged receptor-positive when ≥25% of the tumour cell nuclei stained positive, borderline when 10–25% stained positive, and negative when <10% of the nuclei were positive. Tumours were judged neu-positive when the tumour cells invariably showed unequivocal staining of their membrane with the antibody, and negative when staining was absent. One tumour showed marked heterogeneity, and was labelled indeterminate.

Table 4: **Clinical and pathological characteristics of patients**

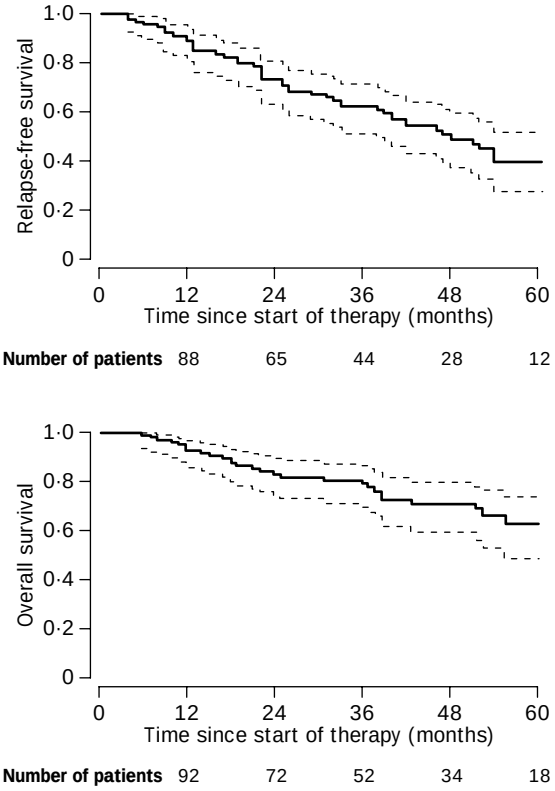

Figure 2: **Relapse-free overall survival for all 97 patients**
Dashed lines=95% CI

Minor and moderate-to-severe lymphoedema of the arm developed in 11 and six patients, respectively, eight of whom had undergone high-dose therapy. No patient developed clinically evident heart failure at any time during protocol treatment.

Overall and progression-free survival

Overall and relapse-free survivals for all 97 patients are shown in figure 2. At the time of the analysis, the median follow-up of the randomised patients was 49 (range 21–76) months. 49 patients relapsed: 19 on high-dose therapy, 19 on conventional therapy, and 11 of the 16 patients. 29 of these patients died from breast cancer: ten on high-dose therapy, 11 on conventional therapy, and eight non-randomised patients. The hazard ratio of relapse-free and overall survival by treatment was 1·05 (95% CI 0·55–1·98) and 0·93 (0·39–2·19), respectively. The two groups were well balanced in terms of prognostic factors before and after up-front chemotherapy (table 4). The relapse-free and overall survival curves for the two groups are shown in figure 3; there were no differences in survival between the two treatment groups.

Univariate and multivariate analyses

The only prognostic factor that approached significance was clinical T stage (p=0·07 for time from randomisation to progression and p=0·10 for survival from randomisation). The addition of high-dose treatment to the models was not significant, nor was adjustment for clinical T stage. The results of the comparison of survival and time to progression by treatment group with stratification by clinical T stage were not significant (similar to the non-stratified comparisons).

Discussion

Our main finding, with a lead-follow-up of over 6 years, is that patients who received high-dose therapy did no better than patients who received conventional chemotherapy in terms of survival. This result conflicts with uncontrolled studies that have suggested substantial survival advantages for patients treated with high-dose therapy, compared with those patients who received standard-dose chemotherapy.[6,7,19,20] Although our study was not designed to detect a small difference in overall or relapse-free survival, it should have easily detected a difference of the size suggested in the seminal paper by Peters and co-workers.[6] With a median follow-up of 2·5 years, the event-free survival in that study was 72% at 3 years, which was significantly better than that of the historical control group (43%). Our power to detect a true relapse-free survival advantage of that size was 80%, so a reasonable assumption is that the relapse-free survival benefit of high-dose therapy is moderate at best and that the results of large multicentre studies that are underway must be awaited before high-dose therapy can be regarded as the standard of care for women with high-risk breast cancer.

The rationale for high-dose therapy comes from laboratory studies that suggested a steep dose-response relation for alkylating agents in breast cancer,[4,5] and from several randomised studies that yielded so-called proof of concept—for example, in non-Hodgkin lymphomas.[21–23] How can the finding of this trial be negative? There are several possible explanations.

First, the high-dose regimen used could be less active

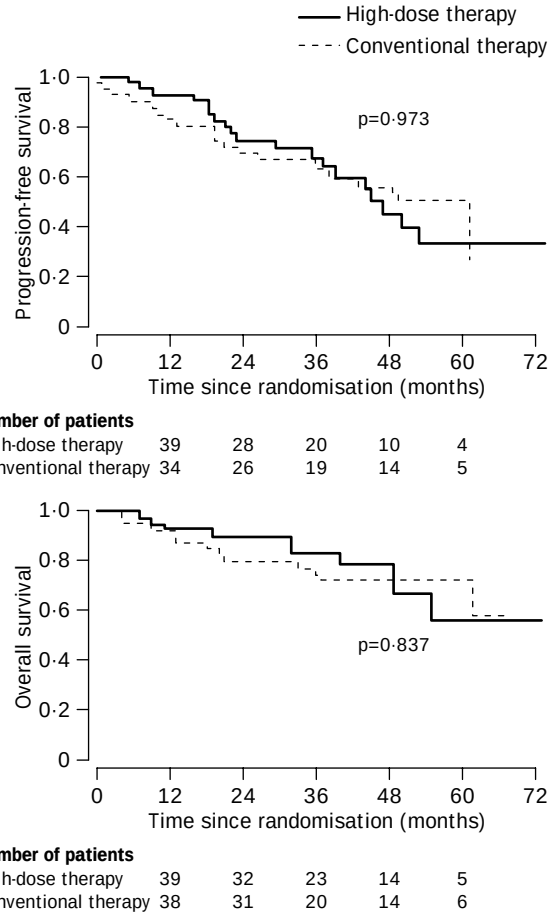

Figure 3: **Progression-free and overall survival**

against breast cancer than the regimens in other studies (notably that of Peters[6]). The combination of high doses of cyclophosphamide, thiotepa, and carboplatin which we used is similar to the well-known CTCb or STAMP-V regimen that is widely used in the USA.[24] The main differences are a slightly lower dose of thiotepa in our regimen than in CTCb (480 mg/m^2 *vs* 500 mg/m^2), but a substantially higher dose of carboplatin (1600 mg/m^2 *vs* 800 mg/m^2). Many of the positive data from the American Bone Marrow Registry have been generated by the STAMP-V regimen,[1] and it is therefore unlikely that our three-drug combination is not appropriate for breast cancer. The CPB regimen used by Peters,[6] originally called STAMP-I,[25] contains slightly less cyclophosphamide than our regimen, a slightly increased dose of cisplatin rather than high-dose carboplatin, and carmustine rather than thiotepa. Similar to cisplatin, carboplatin is an active drug at standard dose in advanced breast cancer, particularly when given as first-line chemotherapy;[26,27] the dose can be increased more than with cisplatin, however, because carboplatin is less nephrotoxic and neurotoxic. Similarly, thiotepa is given at about ten times its standard single-agent dose in our high-dose regimen, whereas the carmustine in the CPB regimen is given at only two to three times its standard dose. Hence, that our high-dose regimen could be inferior to other widely used regimens for breast cancer, including CTCb and CPB, is unlikely.[28]

A second explanation is that the selection of patients may have been less favourable than in other studies of adjuvant high-dose therapy. We enrolled patients who had extensive lymph-node metastases to the axilla, as shown by a tumour-positive infraclavicular node biopsy. This group of patients has a poor prognosis, and the 5-year disease-free survival was less than 25% in a previous randomised study reported from our institute.[29] In addition, the patients in this study were less extensively staged than those in some other studies of high-dose chemotherapy. We did not undertake bone-marrow biopsies or computed-tomography scans of the liver and the brain, and some patients may have had metastatic disease on these investigations.[30] The effect of bias from the selection of patients on the results of uncontrolled studies with high-dose therapy in breast cancer has been documented in studies by Rahman and colleagues[31] and García-Carbonero and colleagues.[32]

A third possibility is that the control treatment in this study was fairly aggressive. The control treatment included up-front chemotherapy with a regimen that contained a high-dose of an anthracyclin (epirubicin at roughly double the standard dose) and a response to chemotherapy did not lead to more conservative surgery. The control treatment also included extensive radiation therapy and tamoxifen. Bartelink and colleagues[33] showed that tamoxifen is more important for survival than chemotherapy in locally advanced breast cancer. In fact, our data on relapse-free and overall survvial for all 97 patients and the 41 controls, were substantially better than survival in a similar group of patients treated in our institute 10–15 years ago.[29] Thus, our study design meant that the effect of the high-dose regimen compared with conventional therapy was difficult to prove. We believe that such a study design is appropriate, since high-dose therapy should not be used if the same results can be achieved by far simpler means.

A final explanation for the negative result is that there is an advantage of high-dose therapy over conventional therapy, but this advantage may be slight. Peters' finding[6] of an improvement in relapse-free survival at 3 years from 43% to 72% corresponds to a reduction of the odds of relapse of 51%. This effect is much greater than what conventional chemotherapy can achieve compared with no adjuvant therapy at all in breast cancer (here, the figure is usually about 25%).[34] Our study was not large enough to exclude a reduction of odds of relapse of up to 40%.

Our primary aim was to develop a practical approach that could be used in a multicentre study of high-dose therapy in women with high-risk breast cancer. The resulting multicentre study was designed for pre-menopausal patients with four or more axillary lymph-node metastases, and began in Jaunary, 1994; the ten Dutch centres collaborating in the study randomised 370 patients in its first 43 months.[8] That study will continue until 880 patients have been randomised and should provide 90% power to detect a true survival advantage of 10%. Several other large studies are in progress on both sides of the Atlantic, including a large Intergroup study that had recruited over 900 patients in May, 1997.[7] Both studies should be able to report first preliminary results by the end of the century.

Little is known about the long-term effects of high-dose therapy, which may include myeloproliferative syndromes, second cancers and, as we have previously shown, potentially non-reversible neuropsychological sequelae.[35] Since high-dose adjuvant therapy did not even yield minimum evidence of a survival advantage over optimum conventional therapy and was associated with severe toxic effects, we strongly believe that this therapy should be given only in the setting of a randomised clinical trial.

Contributors

This study was the result of an intensive multidisciplinry collaboration. Sjoerd Rodenhuis and Dick J Richel designed the protocol and were responsible for the clinical care of the patients together with Elsken van der Wall, Joke W Baars, and Jan H Schornagel. Caro E Koning designed the radiotherapy part of the study and coordinated the radiation therapy together with Jacques H Borger. The surgical part of the study was coordinated by Emiel Rutgers. Willem J Nooijen supervised the haemaphereses as part of the stem-cell mobilisation and harvest procedures that had been developed by Dick J Richel. Otilia Dalesio was the primary statistician and Roel Bakx the data manager. Johannes L Peterse reviewed all pathology specimens. Elsken van der Wall did several analyses, pertaining to feasibility as part of her PhD thesis. Dick J Richel contributed seven patients from the Medisch Spectrum Twente after his move to that hospital. Sjoerd Rodenhuis supervised the conduct and analysis of the study and wrote the article, to which all other authors contributed.

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