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## Original Paper

# The Toxicity of Radiotherapy Following High-dose Chemotherapy With Peripheral Blood Stem Cell Support in High-risk Breast Cancer: A Preliminary Analysis

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**High-dose chemotherapy with autologous bone marrow and/or peripheral blood stem cell (PBSC) support is increasingly employed in the adjuvant treatment of high-risk breast cancer. Subsequent radiotherapy has been reported to be associated with morbidity and mortality resulting from pulmonary toxicity. In addition, the course of radiation therapy may be hampered by excess myelosuppression. The aim of this study was to investigate the contribution to radiation-induced toxicity of a high-dose chemotherapy regimen (CTC) that incorporates cyclophosphamide, thiotepa and carboplatin, in patients with high-risk breast cancer. In two randomised single institution studies, 70 consecutive patients received anthracycline-containing adjuvant chemotherapy (FEC: 5-fluorouracil, epirubicin and cyclophosphamide) followed by radiotherapy to achieve maximal local control. Of these patients, 34 received high-dose CTC with autologous PBSC support. All patients tolerated the full radiation dose in the planned time schedule. Radiation pneumonitis was observed in 5 patients (7%), 4 of whom had undergone high-dose chemotherapy ($P = 0.38$). All 5 responded favourably to prednisone. Fatal toxicities were not observed. Myelosuppression did not require interruption or untimely discontinuation of the radiotherapy, although significant reductions in median nadir platelet counts and haemoglobin levels were observed in patients who had received high-dose chemotherapy ($P = 0.0001$). The median nadir of WBC counts was mildly but significantly decreased during radiotherapy ($P = 0.01$). Red blood cell or platelet transfusions were rarely indicated. Adequate radiotherapy for breast cancer can be safely administered after high-dose CTC with autologous PBSC support. Radiation-induced myelotoxicity is clearly enhanced following CTC, but this is of little clinical significance. Radiation pneumonitis after high-dose therapy may occur more often in patients with a history of lung disease or after a relatively high radiation dose to the chest wall. Other high-dose regimens, particularly those incorporating drugs with known pulmonary toxicity (such as BCNU), may predispose patients to radiation pneumonitis.**


**Key words: high-risk breast cancer, high-dose chemotherapy, adjuvant, radiation penumonitis, haematologic toxicity**

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## INTRODUCTION

THE ABILITY of adjuvant high-dose chemotherapy with autologous bone marrow support to improve long-term disease-free and overall survival in young patients with high-risk breast cancer has become a subject of intensive research [1–3]. The high-dose chemotherapy regimen is usually part of a combined modality approach and is preceded by an anthracycline-based induction chemotherapy and followed by radiotherapy. The benefit of the addition of radiotherapy to adjuvant chemotherapy, with regard to both local disease control and overall survival, has been well established [4–6].

In the largest published study of adjuvant high-dose chemotherapy and radiotherapy in high-risk breast cancer, enthusiasm about the efficacy of this regimen was somewhat tempered

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by substantial toxicity, that led to a 12% toxic death rate [1]. Pulmonary toxicity, occurring 1–6 months following the high-dose consolidation programme, developed in 26 patients (31%) and proved to be fatal in 2 [1]. In 7 of 26 patients, pulmonary toxicity developed during locoregional radiation therapy and required prolonged treatment interruptions or discontinuation before the full dose could be given [1, 6]. 4 additional patients could not receive the planned radiotherapy because of profound bone marrow suppression [6, 7].

It is reasonable to assume that the pulmonary and the haematological toxicities mentioned above result from the interaction of the high-dose drug regimen with the radiation techniques employed. In addition, these toxicities may possibly be enhanced by the treatment schedule and the anthracycline-based induction chemotherapy. The severity of radiation damage to the lungs has principally been related to technical factors, including the volume of lung tissue irradiated, the total dose and rate of its delivery, and the quality of radiation [8, 9]. Animal studies have suggested that preceding chemotherapy may potentiate the damaging effects of radiation to the lung [10]. Clinical data on the additive role of chemotherapy in radiation-induced pulmonary toxicity are scarce [9], and the importance of its dose for this effect is as yet unknown.

Since BCNU (carmustine) is well known for its pulmonary toxicity [11–19], it is conceivable that its use in a high-dose chemotherapy regimen, such as in the study of Peters and colleagues [1], could contribute to the lung damage [18, 19]. In addition, the subsequently administered dose of radiotherapy, including a boost to the mastectomy scar, could have enhanced previous subclinical pulmonary drug toxicity.

Since 1991, patients with high-risk breast cancer in the Netherlands Cancer Institute have been randomised to receive high-dose chemotherapy with peripheral blood stem cell (PBSC) support following anthracycline-based chemotherapy. The high-dose regimen contains carboplatin, thiotepa and cyclophosphamide (CTC), a combination which has not been associated with pulmonary toxicity [20, 21], even when administered repeatedly [22]. Following CTC, all patients received radiation therapy.

We have analysed the first 70 patients with respect to the occurrence of pulmonary and haematological toxicity. Due to the randomisation of the study, the contribution of the high-dose chemotherapy regimen to the development of both types of toxicity could be investigated.

## PATIENTS AND METHODS

From March 1991 until February 1995, 70 patients with high-risk breast cancer in the Netherlands Cancer Institute received a combined modality treatment regimen in two randomised studies evaluating the role of high-dose chemotherapy. 54 patients with high-risk breast cancer, based on a tumour-positive apical axillary lymph node biopsy, were randomised in a single institution trial which started in March 1991 (Figure 1a). 16 additional patients with breast cancer and four or more axillary lymph node metastases were treated according to a Dutch national study in which the first patient was entered in January 1994 (Figure 1b). For both studies, patient accrual is still ongoing.

Both clinical studies were approved by the Institutional Protocol Review Committee and by the Institutional Committee on Medical Ethics. Written informed consent was obtained from all patients according to institutional guidelines.

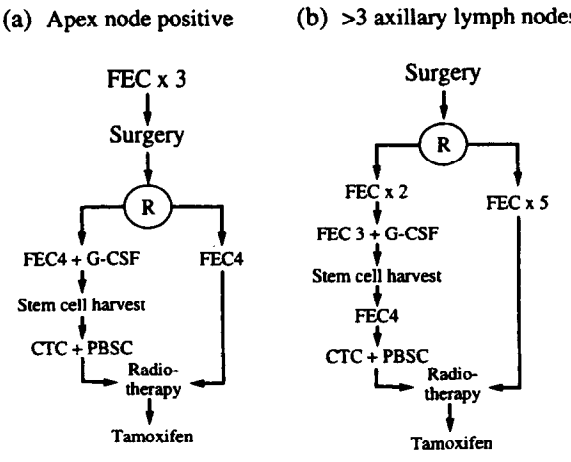


**Figure 1. Outline of the two randomised studies of adjuvant chemotherapy (see text for details). Study (a): patients with breast cancer with metastases to the apical axillary lymph node. Study (b): patients with breast cancer with metastases in four or more axillary lymph nodes. FEC, 5-fluorouracil, epirubicin and cyclophosphamide; G-CSF, granulocyte-colony stimulating factor; CTC, cyclophosphamide, thiotepa and carboplatin; PBSC, peripheral blood stem cell support; R, randomisation. Figures indicate the number of chemotherapy cycles.**

*Patients*

All patients had histologically confirmed stage II-IIIB adenocarcinoma of the breast, and at least four involved axillary lymph nodes, but no distant metastases. All were under 60 years of age, and their WHO performance status was 0 or 1. Staging procedures included a chest roentgenogram, an ultrasound examination of the liver, a radionuclide bone scan and full examination of haematological and biochemistry values. Adequate renal and hepatic functions were required, with a creatinine clearance of $\geq$60 ml/min and a serum bilirubin of $\leq$25 μmol/l. A white blood cell (WBC) count of $\geq 4.0 \times 10^9$/l and a platelet count of $\geq 100 \times 10^9$/l were required. Patients were ineligible if they had a history of prior or concomitant cancer of another site or organ or if they had any disorder that might interfere with adherence to the intensive regimen (e.g. cardiac or pulmonary malfunctioning). No prior chemotherapy or radiotherapy was allowed.

*Treatment regimen*

In the Netherlands Cancer Institute, all patients with clinically operable breast cancer, except those with T1N0 disease, undergo a biopsy of the homolateral apical axillary lymph node before definitive surgery [23]. If a frozen section shows metastatic disease, no further surgery is performed at that time and the patients receive three cycles of FEC-chemotherapy (see below for regimen). If a subsequent tumour response is observed [24], as measured by clinical evaluation, mastectomy or breast conservative surgery (BCS) with axillary clearance is then performed. A clinical tumoral diameter of 5 cm or less is considered acceptable for BCS, providing this will result in an acceptable cosmetic outcome. Subsequently, patients are randomised to a fourth course of FEC-chemotherapy followed either by high-dose CTC-chemotherapy (see below) with PBSC support, radiotherapy and 2 years of tamoxifen or by radiotherapy and tamoxifen alone (Figure 1, Study (a)).

Patients with operable breast cancer and no axillary apex lymph node metastases received definitive surgery. When

pathological examination reveals metastatic involvement of four or more axillary lymph nodes, randomisation to a Dutch national study for high-risk breast cancer is offered (Figure 1, Study (b)). With the exception of the time of surgery, the outline of this study is similar to that of Study A, including the sequence of administration of chemotherapy and radiation therapy.

*FEC-chemotherapy.* All patients received 21-day outpatient cycles of FEC-chemotherapy four times, each cycle consisting of a relatively high dose of epirubicin (120 mg/m$^2$ in Study (a), 90 mg/m$^2$ in Study (b), Figure 1) and 5-fluorouracil (500 mg/m$^2$) and cyclophosphamide (500 mg/m$^2$), all administered by i.v. push [21]. Patients randomised to the control arm of the study received a fifth cycle of FEC-chemotherapy instead of high-dose CTC-chemotherapy.

*High-dose CTC-chemotherapy.* The high-dose chemotherapy regimen was divided over 4 consecutive days (day −6 to day −3) and consisted of cyclophosphamide 1500 mg/m$^2$/d administered as a 1-h intravenous infusion together with a continuous infusion of 3 gram mesna per day, thiotepa 120 mg/m$^2$/d divided between 2 1-h intravenous infusions, and carboplatin 400 mg/m$^2$/d given as a 2-h infusion [20].

Reinfusion of autologous PBSC took place on day 0. Granulocyte-colony stimulating factor (G-CSF) (filgrastim; neupogen®, received as a gift from Amgen-Roche Breda, The Netherlands) at a dose of 300 μg irrespective of body weight, was routinely administered following reinfusion until the WBC count in the peripheral blood exceeded $5.0 \times 10^9$/l [25].

*Stem cell mobilisation and harvest.* The methods used for the mobilisation and harvest of haematopoietic progenitor cells have been described in detail elsewhere [25]. The third (Figure 1, Study (b)) or fourth (Figure 1, Study (a)) FEC-chemotherapy cycle was used to induce mobilisation of PBSC employing a daily dose of 300 μg G-CSF subcutaneously. The size of the stem cell harvest was determined, based on the number of CD34$^+$ cells/kg obtained. A number of $\geq 3.0 \times 10^6$ CD34$^+$ cells/kg body weight was considered sufficient for transplantation [25].

*Supportive care.* The supportive care measures employed during high-dose chemotherapy have been reported previously [20, 21]. Patients received selective bowel decontamination, prophylactic antibiotics against *Streptococci* and fungistatics. Blood products were irradiated before transfusion.

*Radiotherapy.* Radiotherapy was initiated as soon as possible after the chemotherapy had been completed, i.e. within 4 weeks after the last FEC-course in the control treatment arm and within 8 weeks following high-dose CTC-chemotherapy, provided that adequate bone marrow recovery had been obtained (WBC $\geq 3.0 \times 10^9$/l and platelets $\geq 75 \times 10^9$/l) and no other treatment related toxicity was present.

*Internal mammary nodes.* The course of radiotherapy included irradiation of the ipsilateral internal mammary nodes with a radiotherapy field extending from 2 cm above the sternal notch down to the fifth intercostal space with a field 6 cm wide (1 cm hetero- and 5 cm homolaterally from the midline). If the internal mammary node scan showed crossing over, the radiation field was adjusted accordingly. The radiation dose consisted of 50 Gy in 5 weeks in 25 fractions, using a combination of photon beams (Cobalt 60 or 6–8 MV linear accelerators, specified at 2 cm depth) and electron beams (10–14 MeV, specified at Dmax {= 100%}), 2 Gy per fraction, 12 and 13 fractions, respectively.

*Axilla and McWhirter fields (supra- and infraclavicular region.* Field borders extended between vertebral pedicles and insertion of the M. pectoralis major in mediolateral direction and between 4 and 5 cm above the sternoclavicular joint and the sternal insertion of the third rib): in Study (a) (Figure 1), all patients received irradiation to the McWhirter fields with a dose of 50 Gy in 5 weeks, in 25 fractions with a daily dose of 2 Gy. In the patients with metastases to the axillary lymph nodes (Figure 1, Study (b)), indications for irradiation to the McWhirter region included irradiation at the primary tumour site or extensive axillary lymph node involvement. Axillary radiation was not mandatory and left to the discretion of the radiotherapist. The dose was specified at a depth of 2 cm in the medial part. For the lateral axilla, the dose was calculated on the midline of the axillary region.

*Breast.* Following BCS, the whole breast was irradiated with a minimum dose of 50 Gy in 25 fractions, 2 Gy per fraction, at the intersection of the beam axes in the central plane. Minimum and maximum dosage in the central plane were >95% and <110%. A 15 Gy boost dose was administered on a field containing the tumorectomy area, either by interstitial implant or by external irradiation through electron or megavoltage photon beams.

*Thoracic wall.* In patients with apex-node positive disease (Figure 1, Study (a)) having received a mastectomy, the chest wall was irradiated to a dose of 40 Gy in 20 fractions, 2 Gy per fraction, using electrons with an energy of 6 or 8 MeV, depending on the thickness of the thoracic wall as measured by ultrasound examination. In patients in Study (b) (Figure 1), irradiation to the chest wall was only indicated following a microscopically incomplete resection involving micrometastases in the perimysium of the pectoral muscle. A boost to the mastectomy scar was not administered. Special attention was paid to avoid overlapping of the irradiation fields.

*Hormonal therapy.* Following radiotherapy, all patients, irrespective of their hormone receptor status, received tamoxifen for 2 years, at a dose of 20 mg (pre-existing postmenopausal) or 40 mg (premenopausal) daily (Figure 1).

*Follow-up*

Haematological parameters, i.e. haemoglobin (Hb, mmol/l), WBC count and platelets were determined at the start of radiation therapy and weekly thereafter until 2 weeks following the end of radiotherapy. In the next 12 months, laboratory tests were performed bimonthly. Chest roentgenograms were routinely performed prior to radiotherapy and within 6 months thereafter. If indicated, both haematological and roentgenographic evaluations were performed more frequently.

*Evaluation of pulmonary function*

Pulmonary function tests were conducted only on clinical indication. They were performed with a Jaeger Masterlab (Würzburg, Germany). Spirometry included vital capacity

(VC), forced expiratory volume in 1 second ($FEV_1$), $FEV_1$/VC, and total lung capacity (TLC). Diffusion capacity for carbon monoxide (DLCO) was measured and adjusted for alveolar volume, resulting in the KCO. Individual test results were expressed as a percentage of predicted normal values [26].

*Statistics*

Differences in haematological toxicity following both treatment regimens were calculated using the non-parametric Wilcoxon signed-rank sum (Mann–Whitney *U*) test. *P*-values below 0.05 were considered significant. A chi-square test was performed to study the association between the chemotherapy administered and the occurrence of pulmonary toxicity.

## RESULTS

Between March 1991 and June 1994, 54 patients with apex node positive disease were randomised to Study (a) (Figure 1). Following randomisation, 4 patients refused the allocated high-dose chemotherapy. They were subsequently treated according to the control arm of the study and were analysed as such. Another 16 patients with axillary lymph node metastases were randomised to Study (b) (Figure 1). Thus, a total of 34 patients received the high-dose chemotherapy regimen and 36 patients were treated according to the control arm (Table 1). The median follow-up time, calculated from the end of radiation therapy, is 23 months (range 3–51). Pertinent patient characteristics are shown in Table 1.

*Radiation therapy*

All patients received their full dose of radiation therapy according to the planned time schedule. Toxicities requiring untimely discontinuation or interruption of radiation were not observed. The interval between the last chemotherapy cycle and the start of radiation therapy was significantly longer in patients who had received high-dose CTC-chemotherapy compared with patients in the control arm, with a median time of 7 weeks (range 5–11) versus 4 weeks (range 3–8) respectively, $P = 0.01$ (Table 1).

*Table 1. Patient characteristics*

| | FEC only | HD-CTC |
|---|---|---|
| Number of patients | 36 | 34 |
| Apex node positive (Figure 1, Study (a)) | 30 | 24 |
| Four or more axillary nodes (Figure 1, Study (b)) | 6 | 10 |
| Median age (range) | 45 (27–59) | 41 (24–52) |
| Mastectomy | 30 | 30 |
| Left | 11 | 14 |
| Right | 19 | 16 |
| Breast conservative surgery | 6 | 4 |
| Left | 3 | 2 |
| Right | 3 | 2 |
| Clinical target volumes | | |
| Th + IM + Ax/Supracl | 27 | 28 |
| Breast + IM + Ax/Supracl | 6 | 4 |
| IM only | 3 | 2 |
| Median time between last CT and start of RT (range, weeks) | 4 (3–8)* | 7 (5–11)* |
| Median follow-up time since end of RT (range, months) | 17 (3–40) | 17 (2–36) |

RT, radiation therapy; CT, chemotherapy; FEC, 5-fluorouracil, epirubicin, cyclophosphamide, HD-CTC, high-dose carboplatin, thiotepa, cyclophosphamide; Th, thoracic wall; IM, homolateral internal mammary chain; Ax/Supracl, axilla and supraclavicular nodes.
*$P = 0.001$.

In 2 patients, 1 in both treatment groups, initiation of radiotherapy had to be postponed by 8 and 11 weeks, respectively, due to a persistent fistula which had developed following breast surgery. In both patients, radiotherapy was subsequently administered without complications.

*Haematological toxicity*

*Before radiation therapy.* At the start of radiotherapy, no significant difference was observed in WBC count between patients in the high-dose chemotherapy arm and those in the control arm of both studies (data not shown). The number of platelets and the haemoglobin levels were significantly lower in patients who had received high-dose CTC-chemotherapy, with a median platelet count of $184 \times 10^9$/l (range 32–330) and a haemoglobin level of 6.5 mmol/l (median, range 5.5–8.0) in this group of patients compared with median values of $337 \times 10^9$/l (range 87–562) and 7.6 mmol/l (range 5.5–8.4), respectively in patients treated according to the control arm ($P = 0.0001$ for both, Figures 2a and 3a).

*During radiotherapy.* During radiotherapy, the nadirs of the number of platelets and of the haemoglobin level continued to be significantly lower in the high-dose chemotherapy patients. In this group, the median nadir platelet count was about half that in the control patients: $125 \times 10^9$/l (range 18–245) and $248 \times 10^9$/l (range 148–342), respectively, $P = 0.001$ (Figure 2b). The haemoglobin was similarly decreased showing median values of 6.6 mmol/l (range 4.9–8.1) in the high-dose chemotherapy arm and 8 mmol/l (range 6.7–9.6) following FEC-chemotherapy, $P = 0.0001$ (Figure 3b). During radiotherapy, patients who had received the CTC-chemotherapy, also had lower WBC count nadirs, with a median value of $3.6 \times 10^9$/l (range 1.4–5.6) versus $4.4 \times 10^9$/l (range 2.7–7.3) in the control arm, $P = 0.01$ (data not shown). 4 patients in the high-dose chemotherapy arm required transfusion of 2 units of red blood cells. Transfusion of platelets were not given. In none of the patients did haematological toxicity influence the course of the radiation therapy.

*After radiation therapy.* In all patients, laboratory values were determined in the period between 8 and 12 weeks following radiation therapy. At this time, the median WBC counts were similar in both patient groups: $4.8 \times 10^9$/l (range 1.3–8.5) in the high-dose chemotherapy arm versus $5.2 \times 10^9$/l (3.4–11.1) in the control arm (data not shown). The significant differences in numbers of platelets and haemoglobin levels persisted in favour of the patients having received FEC-chemotherapy only, with a median platelet count of $265 \times 10^9$/l (range 174–452) and haemoglobin level of 7.9 mmol/l (median, range 7.1–8.8) in this group of patients compared with median values of $171 \times 10^9$/l (range 17–295) and 7.2 mmol/l (range 5.3–8.4), respectively in the high-dose chemotherapy group ($P = 0.0001$ for both Figures 2c and 3c). A platelet count of $17 \times 10^9$/l was observed in 1 patient who experienced a secondary graft failure following autotransplant due to the development of a myelodysplastic syndrome. Except for this patient, transfusions of platelets were not required.

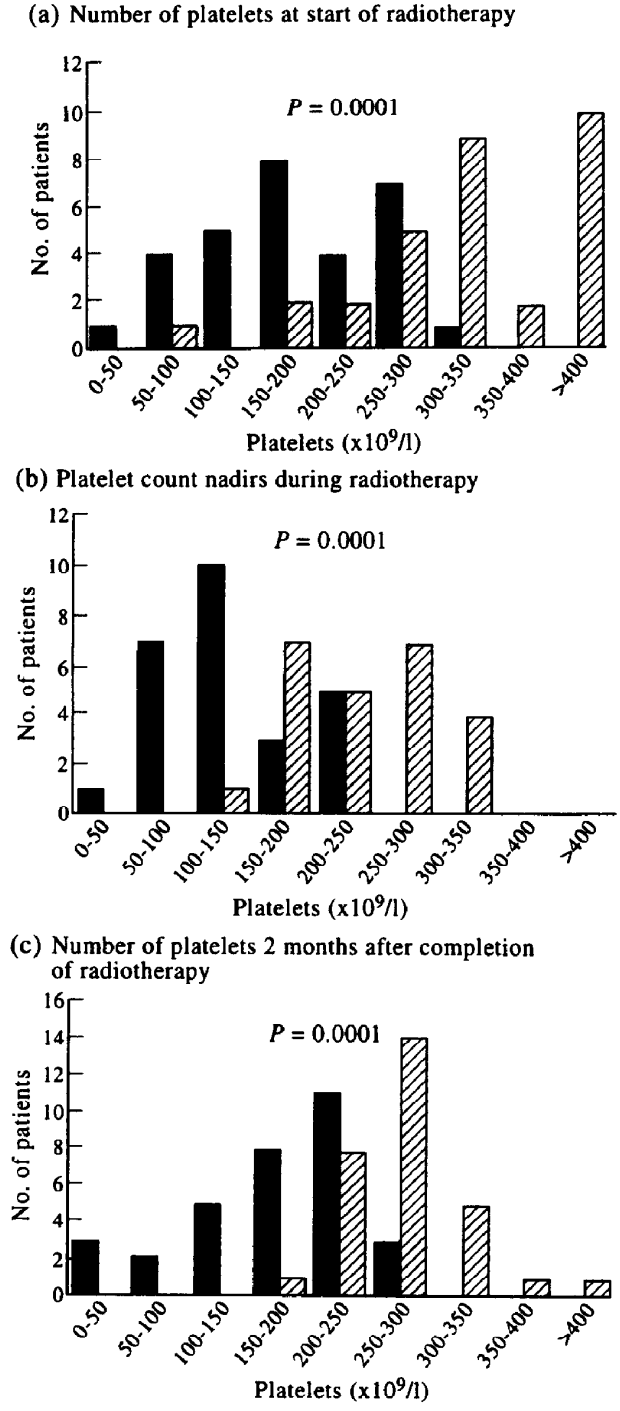


**Figure 2. Effect of radiotherapy on platelet counts following high-dose CTC-chemotherapy (solid bar) or FEC-chemotherapy (hatched bar).**

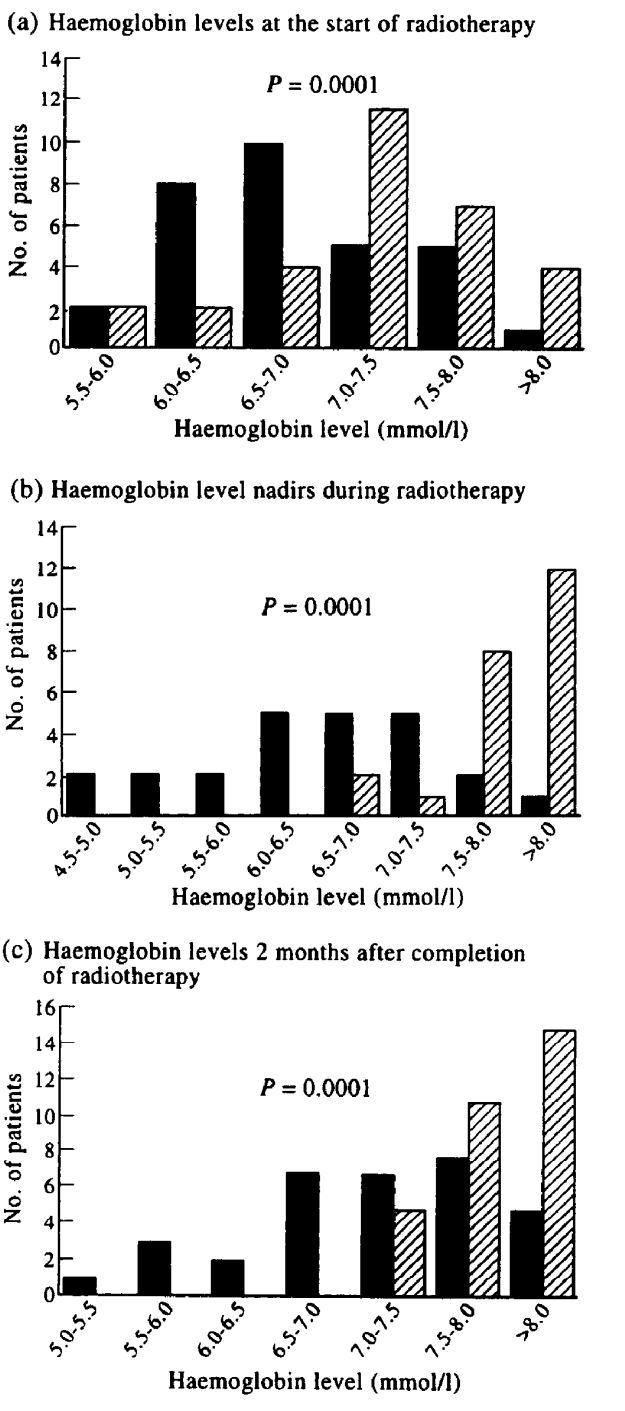


**Figure 3. Effect of radiotherapy on haemoglobin levels following high-dose CTC-chemotherapy (solid bars) or FEC-chemotherapy (hatched bars).**

*Haematological toxicity and the number of PBSCs reinfused*

In patients having received high-dose CTC-chemotherapy with PBSC support, the haematological toxicity occurring during and following radiation therapy appeared to be unrelated to the number of progenitor cells reinfused, as determined by the number of $CD34^+$ cells and the number of colony-forming units of granulocytes and macrophages (CFU-GM) (data not shown) [25].

*Pulmonary toxicity*

*During radiation therapy.* While on radiotherapy, no patients complained of shortness of breath or coughing, nor were there any other signs of pulmonary toxicity at physical examination.

*After radiotherapy.* 5 patients (7%) developed the typical syndrome of radiation pneumonitis, consisting of shortness of breath (grade 2 at the maximum, according to the EORTC late effects scoring system), coughing (grades 1–2), hazy pulmonary infiltrates on the chest roentgenogram and a marked reduction in diffusion capacity as demonstrated by pulmonary

function tests (grades 2–3). All had undergone a mastectomy. 4 patients had received high-dose CTC-chemotherapy with PBSC.

Of these patients, 2 developed symptoms within 2 months of their last radiation session. 1 patient had a history of chronic bronchitis, but did not receive any medication at that time. Both patients were treated with corticosteroids for a period of 10 months after which their clinical symptoms had completely resolved. At that time, only a minor reduction in diffusion capacity still persisted with slight fibrotic changes on the chest roentgenograms where previously infiltrates had been observed. Both patients had received a higher than planned dose of radiation to the thoracic field: 50 Gy rather than the 40 Gy as prescribed by the protocol.

The third patient who had received the high-dose chemotherapy regimen followed by a correct dose of radiation, developed the syndrome of radiation pneumonitis 10 weeks after the end of radiotherapy. She was successfully treated with corticosteroids over a period of 9 months. Clinical symptoms, pulmonary function and roentgenographic abnormalities all resolved.

The fourth patient started to complain about shortness of breath and coughing 3 weeks after the end of radiotherapy. A chest roentgenogram showed pulmonary infiltration in the radiation field and a pulmonary function test revealed a marked reduction in diffusion capacity, i.e. KCO 65% of that predicted. Although all parameters gradually improved, treatment with corticosteroids was still required one year following its initiation. Reduction of the dose of corticosteroids below 10 mg per day induced a recurrence of the symptoms of radiation pneumonitis. As a consequence, treatment with low-dose corticosteroids had to be prolonged.

The fifth patient had been treated in the control arm of the study when she developed rapidly progressive shortness of breath and a dry cough, starting 6 weeks following the completion of radiotherapy. She had been irradiated at the right parasternal field with 8 MV photons specified at 2 cm depth to a dose of 24 Gy, in fractions of 2 Gy. The remaining 26 Gy was delivered by orthovoltage (250 kV), specified at 2 cm depth (fraction dose 1,7 Gy, RBE-correction for orthovoltage). The thoracic field, measured 20 by 20 cm, was irradiated with 6 MeV electrons to a total dose of 40 Gy, in fractions of 2 Gy. At the McWhirter fields, a dose of 50 Gy was administered, in 25 fractions with a daily dose of 2 Gy. She had a history of chronic obstructive pulmonary disease for which she had frequently received prednisolone and antibiotics in the previous years. At the time she developed the radiation pneumonitis, she was not on any of these medications. Laboratory tests for pulmonary viral infections proved to be negative. She was immediately treated with oral prednisolone at a daily dose of 60 mg. Clinical and roentgenographic improvement was rapidly obtained and treatment with prednisolone was discontinued within 5 months. In the subsequent 2 year follow-up, she received 10-day courses of oral prednisolone in combination with antibiotics four times to resolve exacerbations of her obstructive pulmonary disease. The frequency of exacerbations has not increased after the radiotherapy, and during follow-up her pulmonary function tests remained unchanged.

Although radiation pneumonitis developed more frequently in the high-dose chemotherapy group (4/34) than in the control group (1/36), this difference was not statistically significant, $P = 0.349$.

Additionally 7 patients, 3 of whom had received the high-dose chemotherapy, complained of cough without dyspnoea, which occurred 4 weeks to 4 months following the completion of radiotherapy. They had all received a correct radiation dose. Minor abnormalities on chest roentgenograms compatible with radiation fibrosis were observed in 4 patients, including the 3 patients who had received high-dose chemotherapy. In these patients, pulmonary function tests were not performed. Treatment with corticosteroids was not instituted and the clinical symptoms resolved spontaneously in all.

The pulmonary toxicity appeared to be unrelated to the side of radiotherapy, i.e. left or right thoracic wall, to the habit of smoking, or to the degree of skin toxicity (data not shown).

*Radiation pneumonitis and haematological toxicity*

A high erythrocyte sedimentation rate, varying from 89 to 136 mm/h, was found in all 5 patients who had developed radiation pneumonitis. In 3 patients, all other haematological parameters were within the normal range. Haemoglobin levels of 5.6 and 5.8 mmol/l, WBC counts of 2.1 and $2.3 \times 10^9$/l and platelet counts of 35 and $78 \times 10^9$/l, respectively, were found in the 2 remaining patients. They had developed the radiation pneumonitis 3 and 5 weeks after the end of radiotherapy, when their blood counts were still recovering.

*Skin toxicity and mucositis*

In general, the cutaneous side-effects of the radiation therapy were modest. In both treatment arms, 9 patients (about 25% in each treatment arm) developed skin toxicity with erythema and dry desquamation (EORTC grade 1). During radiotherapy, soreness of the throat (EORTC grade 1–2) occurred in about half of the patients in both treatment arms and was readily relieved by the use of polysilane gels. No mucositis was otherwise observed.

## DISCUSSION

High-dose chemotherapy with autologous bone marrow transplantation or with haematopoietic progenitor cell support is increasingly employed as a component of adjuvant therapy in high-risk breast cancer. Several randomised phase III studies, both in Europe and in the U.S.A. [1–3, 19], are currently in progress that should establish by the end of the century whether the considerable cost and toxicity of this treatment modality are justified.

Apart from the main question of whether high-dose therapy can eradicate micrometastases from breast cancer where standard-dose chemotherapy cannot, a number of other important uncertainties remain that must be addressed by these studies. It is, for example, unclear which of the currently available high-dose chemotherapy regimens is the most favourable one, both in terms of efficacy and in terms of toxicity. Toxicity of the regimen is clearly a major issue. In the landmark study by Peters and colleagues [1], treatment related mortality was 12% and many of the toxic deaths may have occurred as a result of the interaction between the high-dose chemotherapy regimen and the radiation therapy. The ability of radiation therapy to achieve local control in breast cancer is critically dependent on the delivered dose and schedule. Because of haematological or pulmonary toxicity, the radiation therapy had to be interrupted or even stopped in a non-significant proportion of patients in Peters and colleagues' study, thereby potentially compromising the long-term results of the approach [1, 6, 7].

While large numbers of patients and several years of follow-up will be required to analyse possible effects of high-dose adjuvant therapy on survival, the influence of the regimen on radiation-toxicity can be evaluated much earlier. We analysed the data from 70 patients who received adjuvant therapy for high-risk breast cancer. All patients were randomised in two closely related studies in which the only difference between the two treatment arms was the presence or absence of a single course of high-dose therapy (Figure 1). The high-dose regimen employed consisted of CTC, a combination that has not been associated with major pulmonary toxicity [20, 22].

Our data indicate that CTC-chemotherapy followed by PBSC support does not lead to excess radiation toxicity within a median follow-up time of 23 months (range 3–51). Obviously, similar to the efficacy data, a definite answer as to the occurrence of late lung toxicities will have to wait several years. Although 5 patients developed radiation pneumonitis (4 in the high-dose arm and 1 in the control arm of the study), all could be managed effectively with prednisone and no treatment-related mortality occurred. It is tempting to speculate that CTC may lead to less enhancement of radiation-induced lung toxicity than a regimen incorporating high-dose BCNU. In the bone marrow transplantation setting, pneumonitis is known to be the dose limiting toxicity of this agent [14, 16, 19]. A clear relationship between the area under the concentration versus time curve (AUC) of BCNU and the occurrence of pulmonary toxicity has been reported [19]. It has also been proposed that BCNU and cyclophosphamide may mutually enhance their pulmonary toxicities [18]. However, a major role for cyclophosphamide alone is unlikely because both the CTC regimen and the CTCb regimen developed by Antman and coworkers [27–29] have not been associated with lung toxicity.

Apart from the effects of the high-dose therapy, the dose and technique of the radiotherapy may be essential [30, 31]. Of 5 patients with radiation pneumonitis, 2 in our study had erroneously received a radiation dose to the thoracic wall that was significantly higher than that prescribed in the protocol. Another 2 pneumonitis patients, including the 1 in the control group, had a long-standing history of chronic obstructive pulmonary disease that may have predisposed them for pulmonary complications [32, 33].

All patients in the high-dose arm received autologous PBSC support, which may have contributed to a relatively rapid haematopoietic recovery. As expected, the start of radiotherapy after transplantation was nevertheless delayed in the high CTC group compared with the control arm. The degree of bone marrow suppression after radiation therapy was clearly higher in the high-dose chemotherapy arm, but is was clinically of little significance and did not require the interruption or discontinuation of the radiotherapy. Large numbers of haematopoietic progenitor cells can usually be harvested in patients with localised breast cancer who have not previously received chemotherapy [21]. These numbers exceed the yield of a typical autologous bone marrow harvest by one or even two orders of magnitude, and the influence of graft size on haematopoietic reconstitution in these patients is well established [25]. Although speculative at present, it is conceivable that the use of large numbers of circulating progenitor cells in the high-dose therapy patients contributed to improved haematological tolerance of radiation.

In conclusion, CTC-chemotherapy with PBSC support appears to be a suitable high-dose regimen to be used in the adjuvant treatment of patients with high-risk breast cancer. It lacks the pulmonary toxicity that has been reported to occur with certain other regimens and it can safely be followed by radiotherapy to the thoracic wall, which is felt to be important to achieve maximal local control. In the present study, only one patient with apex-node positive breast cancer experienced a local recurrence on the thoracic wall, 3 months after the end of radiotherapy. She was the third patient who had received radiotherapy elsewhere and had erroneously been administered 50 Gy rather than the prescribed 40 Gy to the thoracic wall. Hyperthermia was only temporarily successful and she died of subsequent metastatic disease after another 4 months. In an additional 9 patients, all with apex-node positive disease, distant metastases occurred within a median of 26 months (range 11–40) following apex-node biopsy. 6 died of disease, all within 3 months following first diagnosis of progressive disease. The exact data on disease-free and overall survival of patients treated in Study A will be published in the near future.

The ultimate test of the high-dose CTC regimen will obviously be the survival analyses of the prospective randomised studies that are in progress. This will have to await maturation of the data.


1. Peters WP, Ross M, Vredenburgh JJ, *et al.* High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. *J Clin Oncol* 1993, **11**, 1132–1143.
2. Mulder NH, Sleijfer DTh, De Vries EGE, *et al.* Intensive chemotherapy with autologous bone marrow reinfusion in patients with breast cancer and more than 5 involved lymph nodes. *Proc Am Soc Clin Oncol* 1993, **12**, 104 (Abstr.).
3. Gianni AM, Siena A, Bregni M, *et al.* Growth factor supported high-dose sequential (HDS) adjuvant chemotherapy in breast cancer with ⩾10 positive nodes. *Proc Am Soc Clin Oncol* 1992, **11**, 60 (Abstr.).
4. Overgaard M, Christensen JJ, Johansen H, *et al.* Evaluation of radiotherapy in high-risk breast cancer patients: report from the Danish Breast Cancer Cooperative Group (DBCG 82) Trial. *Int J Radiat Oncol Biol Phys* 1990, **19**, 1121–1124.
5. Griem KL, Henderson IC, Gelman R, *et al.* The five-year results of a randomized trial of adjuvant irradiation therapy after chemotherapy in breast cancer patients treated with mastectomy. *J Clin Oncol* 1987, **5**, 1546–1555.
6. Marks LB, Halperin EC, Prosnitz LR, *et al.* Post-mastectomy radiotherapy following adjuvant chemotherapy and autologous bone marrow transplantation for breast cancer patients with ⩾10 positive axillary lymph nodes. *Int J Radiat Oncol Biol Phys* 1992, **23**, 1021–1026.
7. Marks LB, Rosner GL, Prosnitz LR, Ross M, Vredenburgh JJ, Peters WP. The impact of conventional plus high-dose chemotherapy with autologous bone marrow transplantation on hematologic toxicity during subsequent local-regional radiotherapy for breast cancer. *Cancer* 1994, **74**, 2964–2971.
8. Gross NJ. Pulmonary effects of radiation therapy. *Ann Intern Med* 1977, **86**, 81–92.
9. Lingos TI, Recht A, Vicini F, Abner A, Silver B, Harris JR. Radiation pneumonitis in breast cancer patients treated with conservative surgery and radiation therapy. *Int J Radiat Oncol Biol Phys* 1991, **21**, 355–360.
10. Philips TL, Wharam MD, Margolis LW. Modification of radiation injury to normal tissues by chemotherapeutic agents. *Cancer* 1975, **35**, 1678–1684.
11. Phillips GL, Fay JW, Herzig GP, *et al.* Intensive 1,3-bis(2-chloroethyl)-1-nitrosurea (BCNU), NSC#4366650 and cryopreserved autologous marrow transplantation for refractory cancer. A phase I-II study. *Cancer* 1983, **52**, 1792–1802.
12. O'Driscoll BR, Hasleton PS, Taylor PM, Poulter LW, Gattamaneni HR, Woodcock AA. Active lung fibrosis up to 17 years after chemotherapy with carmustine (BCNU) in childhood. *N Engl J Med* 1990, **232**, 378–382.

13. Aronin PA, Mahaley MS Jr, Rudnick SA, *et al.* Prediction of BCNU pulmonary toxicity in patients with malignant gliomas. *N Engl J Med* 1980, **303**, 183–188.
14. Litam JP, Dail DH, Spitzer G, *et al.* Early pulmonary toxicity after administration of high-dose BCNU. *Cancer Treat Rep* 1981, **65**, 39–44.
15. Muggia FM, Louie AC, Sikic BI. Pulmonary toxicity of antitumor agents. *Cancer Treat Rev* 1983, **10**, 221–243.
16. Cooper JAD, White DA, Matthay RA. Drug-induced pulmonary disease. Part 1: Cytotoxic drugs. *Am Rev Respir Dis* 1986, **133**, 321–340.
17. Lombard CM, Churg A, Winokur S. Pulmonary veno-occlusive disease following therapy for malignant neoplasms. *Chest* 1987, **92**, 871–876.
18. Todd NW, Peters WP, Ost AH, Roggli VL, Piantadosi CA. Pulmonary drug toxicity in patients with primary breast cancer treated with high-dose combination chemotherapy and autologous marrow transplantation. *Am Rev Respir Dis* 1993, **147**, 1264–1270.
19. Jones RB, Matthes S, Shpall E, *et al.* Acute lung injury following treatment with high-dose cyclophosphamide, cisplatin and carmustine: pharmacodynamic evaluation of carmustine. *J Natl Cancer Inst* 1993, **85**, 640–647.
20. Rodenhuis S, Baars JW, Schornagel JH, *et al.* Feasibility and toxicity study of a high-dose chemotherapy regimen for autotransplantation incorporating carboplatin, cyclophosphamide and thiotepa. *Ann Oncol* 1992, **3**, 855–860.
21. van der Wall E, Nooijen WJ, Baars JW, *et al.* High-dose carboplatin, thiotepa and cyclophosphamide (CTC) with peripheral blood stem cell support in the adjuvant therapy of high-risk breast cancer: a practical approach. *Br J Cancer* 1995, **71**, 857–862.
22. Rodenhuis S, Van der Wall E, Ten Bokkel Huinink WW, Schornagel JH, Richel DJ, Vlasveld LT. Pilot study of a high-dose carboplatin-based salvage strategy for relapsing or refractory germ cell cancer. *Cancer Invest* 1995, **13**, 355–362.
23. Van Dongen JA. Subclavicular biopsy as a guideline for the treatment of breast cancer. *World J Surg* 1977, **1**, 306–308.
24. Van der Wall E, Richel DJ, Musumanto YH, *et al.* Feasibility study of FEC-chemotherapy with dose-intensive epirubicin as initial treatment in high-risk breast cancer. *Ann Oncol* 1993, **4**, 791–792.
25. van der Wall E, Richel DJ, Holtkamp MJ, *et al.* Bone marrow reconstitution after high-dose chemotherapy and autologous peripheral blood progenitor cell transplantation: effect of graft size. *Ann Oncol* 1994, **5**, 795–802.
26. Quanjer PH, Andersen LH, Tammeling GJ. Clinical respiratory physiology. *Bull Europ Physiopath Resp* 1983, **19**(Suppl. 5), 11–21.
27. Eder JP, Elias A, Shea TC, *et al.* A phase I-II study of cyclophosphamide, thiotepa and carboplatin with autologous bone marrow transplantation in solid tumor patients. *J Clin Oncol* 1990, **8**, 1239–1245.
28. Antman K, Ayash L, Elias A, *et al.* A phase II study of high-dose cyclophosphamide, thiotepa and carboplatin with autologous marrow support in women with measurable advanced breast cancer responding to standard-dose therapy. *J Clin Oncol* 1992, **10**, 102–110.
29. Ayash LJ, Elias A, Wheeler C, *et al.* Double dose-intensive chemotherapy with autologous marrow and peripheral-blood progenitor-cell support for metastatic breast cancer: a feasibility study. *J Clin Oncol* 1994, **12**, 37–44.
30. Rothwell RI, Kelly SA, Joslin CA. Radiation pneumonitis in patients treated for breast cancer. *Radiother Oncol* 1985, **4**, 9–14.
31. Kaufman J, Gunn W, Hartz AJ, *et al.* The pathophysiologic and roentgenologic effects of chest irradiation in breast carcinoma. *Int J Radiat Oncol Biol Phys* 1986, **12**, 887–893.
32. Gillam PMS, Heaf PJD, Hoffbrand BI, *et al.* Chronic bronchitis and radiotherapy of the lung. *Lancet* 1964, **1**, 1245–1248.
33. Hoffbrand BI, Gillman PMS, Heaf PJD. Effect of chronic bronchitis on changes in pulmonary function caused by irradiation of the lungs. *Thorax* 1965, **20**, 303–308.

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