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Intensive Chemotherapy with Autologous Bone Marrow Transfusion as Primary Treatment in Women with Breast Cancer and More Than Five Involved Axillary Lymph Nodes

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Patients with breast cancer and a high number of involved axillary lymph nodes have a poor prognosis, despite adjuvant chemotherapy. The 5-year disease-free survival (DFS) in this group amounts to 30–40% and the 10-year DFS is only 15–20%. Therefore, new treatment modalities are being sought for this group of patients. The aim of the present study was the evaluation of the efficacy of high-dose chemotherapy combined with autologous bone marrow support. 24 patients with a primary breast cancer with more than five involved axillary lymph nodes received, after surgery, six courses of induction chemotherapy followed by ablative chemotherapy and reinfusion of autologous bone marrow. All patients were premenopausal or less than 2 years postmenopausal. Induction chemotherapy consisted of methotrexate (MTX) 1.5 g/m^2 intravenous (i.v.) and 5-fluorouracil (5-FU) 1.5 g/m^2 i.v. on day 1, prednisone 40 mg/m^2 orally on days 2–14, doxorubicin 50 mg/m^2 i.v. and vincristine 1 mg/m^2 i.v. on day 14. Courses were repeated six times every 4 weeks. 10 patients received cyclophosphamide 7 g/m^2 i.v. and etoposide 1.5 g/m^2 i.v. as intensive regimen, in 14 patients this comprised mitoxantrone 50 mg/m^2 i.v. and thiotepa 800 mg/m^2 i.v. Reinfusion of autologous marrow followed on day 7. Finally, patients received locoregional radiotherapy for extranodal disease and tamoxifen 40 mg daily orally over a period of 2 years. The median age of patients was 42 years, range 29–54. The median number of involved nodes was 10. During induction therapy, fever requiring i.v. antibiotics occurred in 4% of 144 courses, 14% of patients suffered from mucositis WHO grade 2–3, and the other patients had mucositis grade 1. During the ablative chemotherapy, 1 patient died, 6 developed septicaemia, 5 showed mucositis grade 3–4 and the other patients had mucositis grade 1 or 2. In the follow-up, 1 patient died from acute cardiac failure. Reversible radiation-induced pneumonitis occurred in 7 out of 14 irradiated patients; symptoms started directly following radiotherapy and lasted for several weeks, but disappeared in due course. During follow-up, 2 patients with six and > 10 positive nodes, respectively, have relapsed after 18 and 36 months, both in the cyclophosphamide/etoposide regimen. Median observation is 3 years, disease-free survival at 5 years is predicted to be 84%. Intensive treatment in these patients with high numbers of involved axillary lymph nodes is a toxic regimen, but may improve the chance of surviving free of disease.
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INTRODUCTION

FOR PATIENTS with primary breast cancer, the best treatment is surgery, although in many patients the disease will relapse within 5 years, indicating that systemic disease was already present at the time of surgery. The chance of developing metastases is related to a number of tumour characteristics, notably the tumour size, but primarily to the presence of metastases in the axillary lymph nodes [1, 2]. The 10-year disease-free survival in patients with negative axillary nodes is 75%; while the disease-free survival in patients with one to three involved lymph nodes is approximately 30–40%, and in patients with more than three nodes, it ranges from 15 to 20%, despite adjuvant combination chemotherapy [3, 4]. Because this treatment is not curative in most patients, more intensive chemotherapy has been tried, aiming at a greater therapeutic efficacy.

In vitro studies with human tumour cell lines have shown a clear dose–response relationship for alkylating agents, reaching a higher cell kill with higher dosages. The same effect has been shown in patients with metastatic breast cancer [5, 6]. These observations suggest that cytostatic agents given in a high dose

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as an adjuvant therapy could have better results than treatment with standard dosages.

Higher dosages of cytostatic drugs will mean more toxicity to the bone marrow and other organs. The latter effect can be partially prevented by choosing a combination of drugs without overlapping organ toxicities. Marrow toxicity can be curtailed or even prevented by reinfusion of autologous bone marrow, or peripheral stem cells harvested by leucapheresis. Over the years, many studies have been aimed at finding the maximal tolerable doses of combinations of cytostatic agents in combination with autologous bone marrow transfusion (ABMT). Starting in 1986, we have treated premenopausal patients with primary breast cancer and more than five involved axillary nodes, including the apical node, with intensive chemotherapy followed by ABMT. In a previous report, we have shown our data in patients with disseminated and locally advanced disease [7]. We will now update our results in patients with involved axillary lymph nodes, and report on the results of a different ablative regimen.

PATIENTS AND METHODS

Eligible for this study were female patients with histologically proven carcinoma of the breast who underwent curative surgery and had at least five involved lymph nodes, including the apical node. Patients were premenopausal or maximally 2 years postmenopausal and had a good performance score (WHO 0–2). Informed consent was obligatory for the induction treatment as well as the intensified chemotherapy with ABMT. The plan of investigation was affirmed by the ethical committee of the University Hospital Groningen.

Excluded were patients with disturbed liver (serum bilirubin > 30 μmol/l) or renal function (serum creatinine > 120 μmol/l), pulmonary or cardiac afflictions, or another malignancy in the past. Cardiac function was not studied separately, as we found no consequent changes during the previous phase I study with the combination mitoxantrone/thiotepa [8].

Schedule of treatment

Most patients had a modified mastectomy according to Patey. The preoperative screening comprised a physical examination, an electrocardiogram, complete chemistry, chest X-ray, skeletal scintigraphy and liver sonography. Before chemotherapy, bilateral iliac crest biopsies were performed to exclude bone marrow metastases.

The induction chemotherapy comprised two parts, a combination of methotrexate (MTX) with leucovorin rescue, 5-fluorouracil (5-FU) and prednisone, followed after 2 weeks by doxorubicin and vincristine.

MTX, 1.5 g/m^2, was given after alkalising the urine with 1 l of 1.4% sodium bicarbonate intravenously (i.v.) over 8 h. 5-FU 1.5 mg/m^2 was given after MTX, and was followed by sodium bicarbonate 1.4%, 2 l i.v. over 6 h. Oral leucovorin 15 mg was started 24 h after MTX and given every 6 h over 48 h. Patients received oral prednisolone 40 mg/m^2/day over 14 consecutive days. On day 14, the patient received doxorubicin 50 mg/m^2 i.v. and vincristine 1 mg/m^2 i.v. The cycles were repeated every 4 weeks, for a total of six cycles.

Dose reduction was applied for leucocytes $< 2.0 \times 10^9$/l or platelets $< 100 \times 10^9$/l, but not for nadir values. For WHO toxicity grade 3 to 4, apart from myelotoxicity, a dose reduction of 25% was applied.

All patients were restaged after induction treatment, and bone marrow was harvested from both iliac crests after premedication with pethidine 100 mg and diazepam 20 mg intramuscularly (i.m.) and local anaesthesia with lidocaine 1% without general anaesthesia. A minimum of 2×10^8 nucleated cells/kg bodyweight were harvested during this procedure.

Intensive chemotherapy comprised two different schedules: a combination of cyclophosphamide 7 g/m^2 i.v. divided over 3 days, and etoposide 1.5 g/m^2 i.v. in six doses divided over the same 3 days in 10 patients. To prevent haemorrhagic cystitis, mesna 3.5 g/m^2 was given. 14 patients were treated with thiotepa 800 mg/m^2 i.v. and mitoxantrone 50 mg/m^2 divided over 3 days.

All patients were treated in a single room without specific isolation procedures. Based on regular bacteriological screening, selective gut decontamination was applied. Each patient received total parenteral nutrition. The menses were suppressed by lynestrenol. All blood products, infused during the aplastic period, were irradiated to prevent graft versus host disease [9]. For a platelet count $< 20 \times 10^9$/l, autologous platelets were infused, which were harvested by thrombopheresis before the high dose treatment. During the aplastic period, amphotericine and acyclovir were given prophylactically. Seven days after the start of intensive chemotherapy, the autologous bone marrow was reinfused. In case of extranodal tumour growth, patients received locoregional radiotherapy after complete recovery of the bone marrow function. All patients received oral tamoxifen 40 mg/day for a period of 2 years.

RESULTS

Starting from 1986, 24 patients were entered. The median age was 42 years (range 29–54), 3 patients had a T_1 tumour, 10 patients T_2, 7 patients T_3, and 4 patients a primary of unknown size. Histologically, in 6 patients the tumour had invaded the skin or underlying pectoralis muscle (pT4) [8]. In 12 patients, five to 10 axillary lymph nodes were involved and in 12 others more than 10 metastatic lymph nodes were found. 14 patients received locoregional radiotherapy after recovery of the bone marrow for extranodal tumour growth. Median follow-up is now 36 months (range 9–72). 2 patients, 1 with six and 1 with > 10 involved lymph nodes, both treated with the cyclophosphamide/etoposide ablative regimen, developed skeletal metastases after 18 and 36 months, respectively. Projected disease-free survival at 72 months is 84% (Fig. 1).

Toxicity of induction chemotherapy

A total of 144 treatment cycles was given. Nausea and vomiting were mild; they seldom occurred after MTX/5-FU, while

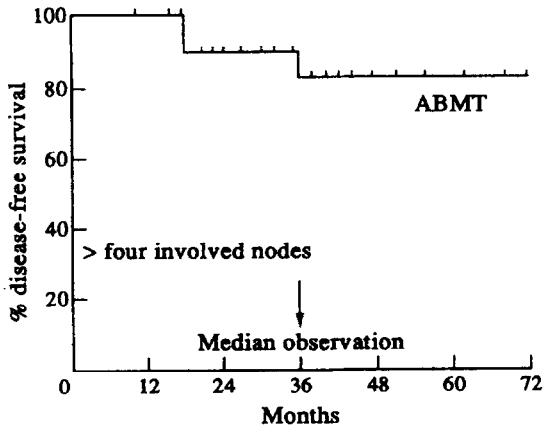

Fig. 1. Disease-free survival in 24 patients treated with intensive chemotherapy and autologous bone marrow transfusion (ABMT). The median observation period is 36 months (range 9–72). The disease-free survival at 72 months amounts to 84%.

doxorubicin was well tolerated using metoclopramide, possibly also as a result of the anti-emetic effect of the prednisolone in the therapy schedule. Mucositis and conjunctivitis were frequent; mucositis more than WHO grade 1 occurred in 14% of cycles, but did not necessitate dose adjustments. The dosage of MTX/5-FU was reduced in 3.1% of cycles for myelotoxicity. Cerebellar toxicity by 5-FU administration, which was fully reversible, necessitated dose adjustment to 50% in 5.1% of all cycles. Hand-foot syndrome occurred regularly, but was tolerable. The dosage of doxorubicin was reduced in 1.4% of all cycles for myelotoxicity, but not for liver or cardial toxicity. Vincristine-induced WHO grade I neurotoxicity occurred in 28% of all patients and vincristine was reduced in 16% of all cycles.

Periods with fever over 38.5°C occurred in 26 cycles (18%). On 23 occasions (16%), out-patient treatment with antibiotics was necessary and on three occasions patients were hospitalised. There was no mortality during induction treatment.

Toxicity of intensive chemotherapy

During administration of high dose chemotherapy, all patients suffered from nausea and vomiting, which was tolerable by administration of the new selective 5-HT_3 antagonists. Mucositis occurred in all patients, WHO grade 1 in 4, grade 2 in 15, grade 3 in 2 and grade 4 in 3 patients.

All patients suffered from total marrow aplasia, as expected. The median periods of leucocyte counts below 1×10^9/l were 13 days (range 10–16) during cyclophosphamide/etoposide and 16 days (range 10–47) after mitoxantrone/thiotepa. Platelet counts below 20×10^9/l were seen for a median period of 11 days (range 5–18) and 21 days (range 11–62), respectively. All patients suffered from one or more periods of fever over 38.5°C. Median days with fever amounted to 9. Severe infections or sepsis occurred in 6 patients; 1 patient died during treatment of an acute respiratory distress syndrome (ARDS). No bleeding complications were seen, nor other forms of organ toxicity. The first 10 patients treated with the first ablative regimen (cyclophosphamide/etoposide) did not receive growth factor support, thereafter patients received either granulocyte colony-stimulating factor (G-CSF) or granulocyte–macrophage CSF (GM-CSF) after bone marrow re-infusion. 1 patient died 3 months after intensive chemotherapy (mitoxantrone-thiotepa) from acute cardiac failure of unknown cause; postmortem examination was denied. An association with doxorubicin and mitoxantrone could not be excluded. Of all 14 patients receiving locoregional irradiation, radiation pneumonitis was seen in 7 patients, which was manifested by a dry cough and exertional dyspnoea directly following radiotherapy, and lasted for several weeks to months. Symptoms subsided gradually and most patients received prednisolone for a period of several weeks.

DISCUSSION

From 1982 onwards, patients with either disseminated breast cancer, testicular cancer, lung or ovarian cancer, for whom no standard treatment was available, have been treated with intensive chemotherapy in combination with ABMT in the University Hospital Groningen [10, 11]. Starting from 1986, this intensive therapy was also applied to patients who had received curative surgery for breast cancer, but in whom the prognosis was considered poor, based on the number of involved axillary lymph nodes. The projected disease-free survival of 84% at 60 months achieved by this treatment seems to be considerably better than the results of adjuvant chemotherapy with the cyclophosphamide, MTX, 5-FU (CMF) combination. In comparable patient groups, this standard treatment will result in a 5-year disease-free survival of only 30–40%, and the 10-year disease-free survival of only 15–20% [3, 4].

Adjuvant treatment with more intense schedules of cytotoxic agents without giving ABMT have been described. In a study of Bonadonna and colleagues, patients with more than three involved lymph nodes were randomised between four cycles of doxorubicin followed by eight cycles of CMF, or a schedule alternating CMF and doxorubicin, reaching the same total dose of each drug. The 5-year disease-free survival of the first treatment amounted to 58%, of the second only to 37% [12]. Buzdar and colleagues reported intensive chemotherapy with cyclophosphamide, doxorubicin, 5-FU, vincristine and prednisone, followed by maintenance therapy with tamoxifen, methotrexate and vinblastine, in patients with four to 10 involved axillary lymph nodes, and found a 7-year disease-free survival of 81% in this group. In the group of patients with more than 10 lymph nodes, this was only 33%. Data on the effect of toxicity on mortality were not stated [13]. Abeloff and colleagues gave intensive therapy to 53 patients with more than 10 metastatic lymph nodes over a period of 16 weeks. After a median follow-up of 17 months, the projected 3-year disease-free survival amounted to 80% [14].

The indication for this intensive treatment in combination with ABMT in patients with a high number of involved lymph nodes is not yet clearly defined, and data in the literature are scarce. Peters and colleagues have published data on 85 patients with more than 10 axillary nodes, with intensive chemotherapy and ABMT, followed by radiotherapy, and found a disease-free survival of 72% after a median follow-up of 2 years (range10–60 months) [15]. The group of Gianni and colleagues reported a study with alternating, non-crossresistant cytostatics in high doses, supported by reinfusion of peripheral stem cells. After a median observation period of 21 months, disease-free survival amounted to 93%, compared with 43% after standard treatment [16]. As yet, there are no data on studies comparing intensive chemotherapy with or without ABMT, but these have been started recently.

The main problem of this intensive therapy of prognostically unfavourable breast cancer patients is the considerable toxicity, the more so in patients without demonstrable tumour activity, which may lead to mortality from treatment instead of from tumour progression. In most studies reported, this treatment carries a mortality of 5–10% [17, 18]. Most fatal complications during intensive treatment are due to neutropenic infections, despite prophylactic gut decontamination [19], antiviral and antifungal medication [20], frequent bacteriological monitoring, and treatment with combined broad spectrum antibiotics in case of fever [10, 11]. This risk may be curtailed by the use of haematopoietic growth factors during the period of aplasia [21]. A further risk reduction may be achieved by the infusion of peripheral stem cells in addition to or instead of ABMT [22]. Although the harvest of bone marrow is usually well tolerated with local anaesthesia and premedication [23], the harvest of peripheral stem cells will probably replace this procedure in the near future.

Haemorrhagic complications during marrow aplasia can be adequately prevented by prophylactic platelet transfusion over the first days, even by autologous platelets [24, 25]. During admission, total parenteral nutrition is given to ensure an optimal nutritional status [26].

The patients who died during and after this treatment illustrate that infection is not the only risk of this approach. 1 patient died in the follow-up phase from acute right ventricular failure

with output failure. An association with the dose of cumulative administered doxorubicin (300 mg/m^2) combined with mitoxantrone could not be dismissed. Evaluation of left ventricle ejection fraction was not studied in this group of patients, as we could not demonstrate regular changes in the previous phase I study combining mitoxantrone and cyclophosphamide or melphalan [9].

The occurrence of radiation pneumonitis in 50% of patients treated is considerably more than after radiotherapy alone. The previous exposure to doxorubicin may play a role in this problem. At present, we are performing a prospective study to evaluate the separate impact of chemo- and radiotherapy. The preliminary retrospective data do not indicate the occurrence of any long-term pulmonary toxicity.

The prognosis of patients with breast cancer and multiple involved axillary lymph nodes is poor when treated by standard surgery, radiotherapy and chemotherapy.

This study suggests that intensive chemotherapy combined with ABMT can improve this prognosis. It should be taken into account that the number of patients treated is still small, and the relative short follow-up period cannot exclude a temporary effect. More certainty on this issue can be obtained only by randomised studies. Comparative studies have been initiated in the U.S.A. in patients with more than 10 metastatic nodes [27]. Recently, a randomised study has been started in the Netherlands to compare the value of intensive treatment with ABMT support with standard adjuvant therapy. Premenopausal patients with more than four involved axillary lymph nodes will receive four cycles of 5-FU, 4-epirubicin and cyclophosphamide (FEC), and will then be randomised to receive another cycle of FEC or intensive chemotherapy with cyclophosphamide, thiotepa and carboplatin, followed by peripheral stem cell support. The results of this and similar studies should determine if high dose chemotherapy will have a definite place in the adjuvant setting.

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