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Neoadjuvant high dose chemotherapy plus peripheral blood progenitor cells in inflammatory breast cancer : a multicenter phase II pilot study

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Background and Objectives. With the introduction of combined modality therapy, approximately 30% of patients wth inflammatory breast cancer (IBC) are alive and free of disease at 5 years, but the lack of control of systemic disease continues to be the main reason for treatment failure. The importance of the response to primary chemotherapy and, in particular, complete tumor regression after primary chemotherapy have previously been described to be among the most reliable prognostic factors along with the dose intensity of doxorubicin.

Design and Methods. To evaluate pathologic response rate and toxicity of neoadjuvant high dose chemotherapy (HDCT) with autologous peripheral blood progenitor cell (PBPC) support in patients affected by IBC, 21 patients were enrolled in a study in which it was planned that they would receive 4 courses of epirubicin 150 mg/m^2 plus granulocyte colony-stimulating factor (G-CSF) as induction and mobilizing chemotherapy. Patients with non-progressive disease were intended to receive 2 consecutive courses of a combination of high doses of mitoxantrone 40 mg/m^2, thiotepa 500 mg/m^2 and cyclophosphamide 200 mg/kg as a conditioning regimen.

Results. PBPC collection was successful in 20/21 patients. Twelve patients received a single course of HDCT, whereas 7/20 patients underwent a double procedure. At a median follow up of 48 months, 20/21 patients were evaluable for toxicity and 19/21 for response. At surgery 4/19 patients (21%) had no evidence of viable tumor cells in the breast and in axillary nodes, while 4 (21%) and 11 patients (58%) had microscopic and macroscopic disease, respectively. Eight patients have relapsed (35%) so far at a median of 16 months (9-54) from diagnosis. Eleven patients remain alive without evidence of disease. Five out of 20 patients experienced severe cardiotoxicity with congestive heart failure (CHF) which was responsible for the only treatment-related death.

Interpretation and Conclusions. This neoadjuvant HDCT regimen seems to be very effective in terms of objective responses, but we observed a high rate of cardiotoxicity and only a few patients were able to receive the two planned courses of high dose chemotherapy.
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Key words: high dose chemotherapy, inflammatory breast cancer, cardiotoxicity.

Inflammatory breast cancer (IBC) is a very rare disease accounting for 1-4% of all breast cancers in Western countries. The prognosis of this peculiar disease is dismal and its clinical course is characterized by a high rate of locoregional and mainly metastatic failures. Overall survival of patients managed with only locoregional treatment did not exceed 5% at 5 years.[1] These poor results led to the introduction of combined modality treatment. The most common approach consists of doxorubicin-based induction chemotherapy followed by regional therapy in the form of surgery, radiotherapy, or both: the role of hormonal therapy remains to be defined. This sequential combination allows chemotherapy to be administered before the possible development of tumor-resistant clones and alteration of tumor vasculature by radiation therapy or surgery, and for the *in vivo* effectiveness of chemotherapy to be evaluated. With the introduction of combined modality therapy, approximately 30% of patients with IBC are alive and free of disease at 5 years,[2] but the lack of control of systemic disease continues to be the main reason for treatment failure. The importance of the response to primary chemotherapy and, in particular, complete tumor regression after primary chemotherapy have been previously described to be among the most reliable prognostic factors[3-6] along with the dose intensity of doxorubicin.[7] Over the last 10 years several trials have evaluated the role of high-dose

chemotherapy (HDCT) with autologous peripheral blood progenitor cell (PBPC) support in the treatment of breast cancer, but these studies have generally not included any patients with inflammatory breast cancer.

On the basis of such considerations, we designed a phase II trial in the attempt to improve tumor response in IBC by increasing both the dose intensity of doxorubicin and the total dose of chemotherapy administered by using high dose chemotherapy and PBPC rescue.

Design and Methods

Eligibility criteria

Patients were eligible for the study if they had clinically and histologically proven non-metastatic IBC, were aged ≤55 years, had an ECOG performance status ≤ 1, adequate renal, hepatic and bone marrow functions (serum creatinine, AST/ALT/bilirubin ≤ 1.25 times higher than the upper limit of normal range, WBC >3000/μL with ANC >500/μL, PLT > 100,000/μL), and echocardiographically estimated resting left ventricular ejection fraction (LVEF) >50%. Exclusion criteria were the presence of other concomitant serious illnesses or an uncontrolled ongoing infection, psychological contraindications to receiving HDCT, and previous malignant tumors. All patients were required to provide written informed consent before entering the study. The baseline evaluation included physical examination, standard biological tests including CEA and Ca 15-3 assays, bilateral mammography, chest X-ray, ECG and echocardiography, radionuclide bone scan, bone marrow biopsy, liver ultrasounds or computed tomography (CT) scan, and CT scan of the brain (only if clinically indicated).

Treatment plan

Induction chemotherapy. We initially planned to administer 4 courses of epirubicin 150 mg/m^2 by intravenous (iv) 4 hours infusion at 14-day intervals. Afterwards, because of the occurrence of some treatment-related cardiac toxic events we decided to omit the fourth course of epirubicin. Granulocyte colony-stimulating factor (G-CSF) 5 μg/kg/day subcutaneously was started 24 hours after chemotherapy and given until hematopoietic recovery. Mobilization of PBPC was performed if possible after the second or the third course of epirubicin. The study design is shown in Figure 1.

PBPC collection. The number of CD34$^+$ cells considered as the target for each high dose chemotherapy course was ≥ 5x10^6/kg/bw. PBPC collection procedures were performed according to an already published method.[8]

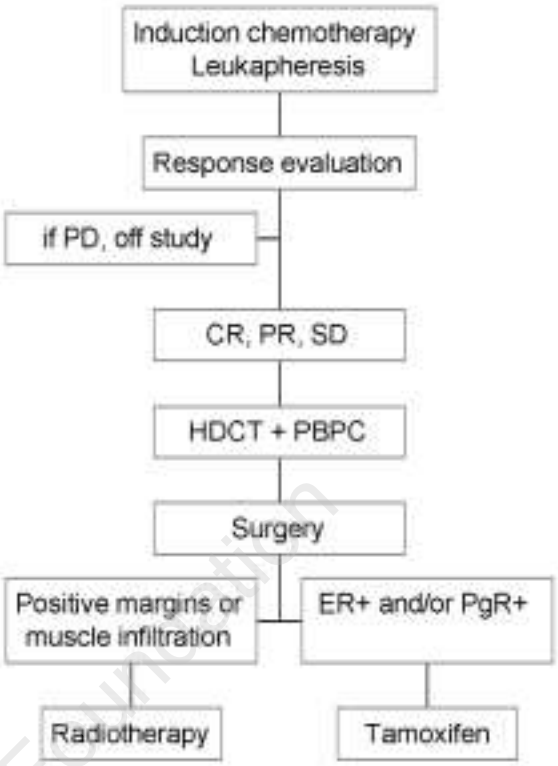

Figure 1. Study design.

High-dose schedule. In patients with non-progressive disease, we planned to administer 2 courses of a combination of mitoxantrone 40 mg/m^2 on day -6, thiotepa 500 mg/m^2 on day –5 and cyclophosphamide 100 mg/kg on days –4 and –3. PBPC as hematopoietic rescue were infused on day 0. Hematopoietic growth factor (filgrastim 5 mg/kg/bw) administration was started 24 hours after PBPC infusion, and continued until the absolute neutrophil (ANC) was higher than 1000/μL for three consecutive days.

Post-chemotherapy treatment. Radical mastectomy was scheduled after recovery from the last high dose chemotherapy course. Chest wall radiotherapy (50 Gy) was given in cases of positive margins of resection and/or infiltration of pectoral muscle. Tamoxifen was administered to estrogen or progesterone receptor positive patients at the dose of 30 mg/day for 2 years. The determination of hormone receptors was performed whenever possible on tissue samples obtained at diagnosis. In all other cases the receptor status was determined from a surgical specimen.

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Response evaluation

Clinical evaluation. Clinical evaluation of the patients was carried out after the induction chemotherapy by physical examination, standard laboratory tests including CEA and Ca 15-3 assays and bilateral mammography. A complete clinical response was defined as clinically complete disappearance of breast inflammation, as well as of the underlying breast tumor mass. A partial response was defined as at least a 50% decrease in tumor diameter with disappearance of inflammation.

Pathologic evaluation. Pathologic response was assessed after surgery. After macroscopic inspection for gross disease, microscopic inspection was performed to look for both residual tumor and stromal alterations such as fibrosis or sclerosis. The whole axillary specimen was assessed for lymph node involvement. Estrogen and progesterone receptor status was also analyzed.

Follow-up. Patients were re-evaluated by physical examination, standard laboratory tests including CEA and Ca 15-3 assays, chest X-ray, and liver ultrasounds 1 month after the stem cell reinfusion and subsequently every 3 months for 2 years and then every 6 months. ECG and echocardiography to assess LVEF were carried out at the first month follow-up and then every six months. Mammography and radionuclide bone scanning were performed once a year.

Statistical analysis

Overall survival (OS) and disease-free survival (DFS) were calculated from the beginning of chemotherapy. OS was defined as the time to death from any cause, whereas DFS was defined as the time to any type of recurrence. The data were summarized as median values and ranges (for continuous variables) and as frequencies and percents (for categorical variables). Survival curves were calculated using the Kaplan-Meier method and compared with the log-rank test.

Results

Patients' characteristics

From August 1994 to December 1998, 21 patients affected by non-metastatic IBC but who had never received chemotherapy were enrolled in the study. Their median age was 46 years (range 29-56); thirteen out of the 21 (62%) patients were premenopausal and performance status was 0 according to ECOG criteria in all patients; median baseline LVEF was 60% (range 50-75%). Twenty out of the 21 patients (95%) were evaluable for response to neoadjuvant chemotherapy and for toxicity. Sixteen patients received 4 courses of epirubicin, whereas in 4 patients the last course was omitted because of the protocol amendment. Twenty out of the 21 patients received the high dose chemotherapy, but only 7 out of 20 patients (35%) received the two planned courses. The reasons for not administering the double graft to 13 out of 20 patients (65%) were the following: inadequate number of $CD34^+$ cells collected in 6 patients, severe gastrointestinal toxicity in one patient, severe lung injury in one patient, congestive heart failure in 3 patients with one toxic death, while 2 patients were considered at high risk of cardiotoxicity after the first high dose chemotherapy course. One patient was not evaluable because she refused to receive any further treatment after a severe chemical phlebitis due to epirubicin extravasation and withdrew from the study.

PBPC collection

Only 11 out of 21 patients (52%) achieved the target number of $CD34^+$ cells with a median of 2 leukapheresis procedures (range 1-4): a single procedure was performed in 6 out of 20 patients (30%), while a double procedure was necessary in 9 patients (45%), 3 procedures in 4 patients (20%) and 4 in one patient (5%). One patient did not mobilize, so underwent bone marrow harvest. A total of 38 leukapheresis were performed between days 8 and 13 after the beginning of chemotherapy (median day 11). The median value of $CD34^+$ cells collected was 12.6×10^6/kg/bw (range 3.2-22.8) per patient, while the median value of $CD34^+$ cells reinfused after each course was 5.9×10^6/kg/bw (range 2.2-11.4).

Treatment response

Among 20 evaluable patients, 4 had a CR (20%), 14 a PR (70%) and 2 stable disease (10%) after induction chemotherapy. At the end of high-dose chemotherapy the response rate increased up to 95% including 11 CRs and 8 PRs. That is to say, 7 PRs converted to CRs and 1 stable disease turned into a PR.

Only 19 out of the 21 patients underwent radical mastectomy because one patient died 30 days after the first course of high dose chemotherapy from cardiac toxicity. At pathologic examination of surgical specimens we observed complete disappearance of disease in 4 patients (21%), presence of microscopic residual disease in 4 more patients (21%) and persistence of either gross disease or positive axillary nodes in the remaining 11 patients (58%). Axillary nodes were involved (median number 4; range 1-12) in 8 patients and the node status was unknown in one patient with residual gross disease.

At a median follow-up of 48 months the OS and DFS of the entire population was 63 and 54 months, respectively [Figure 2]. Eight patients out of 19 (42%)

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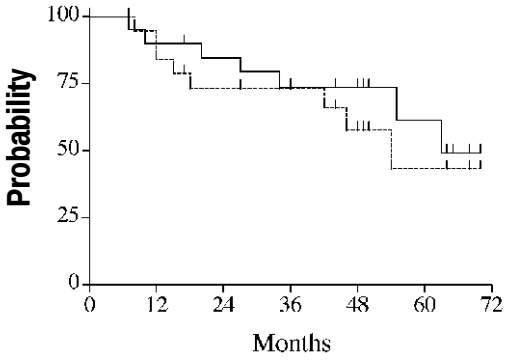

Figure 2. Disease free survival (– – –) and overall survival (———) curves.

have relapsed, six of whom are now dead. Recurrences occurred at locoregional sites (2 patients), distant sites (5 patients) or both (1 patient). Patients whose tumors achieved a pCR to neoadjuvant chemotherapy showed, a slightly better DFS than patients whose tumors responded less favorably, though this difference did not attain statistical significance. The median disease-free survival for node negative patients was 42 months, whereas the median has so far not been reached for node positive patients.

Hematopoietic recovery after high dose chemotherapy

Patients required a median of 9 days (range 6-16) to reach an ANC greater than 500/µL. The median times to reach an unsustained platelet count superior to 20,000/µL and 50,000/µL were 5 days (range 0-32) and 12 days (range 7-32), respectively. The median numbers of platelets and red blood cell transfusions were 12 (range 4-26) and 4 (range 0-8), respectively. The median duration of hospital stay was 24 days (range 15-51). The median number of days with fever > 38 °C was 4 (range 0-8); further infection was documented by blood cultures in 11 patients during the first course and in 5 during the second one. We did not observe any significant differences in terms of hematopoietic recovery between the 2 chemotherapy courses.

Non-hematologic toxicity after high dose chemotherapy

Grade 3-4 nausea and vomiting occurred in 7 out of 20 patients (35%) and in 3 out of 7 patients (43%) after the first and the second graft, respectively, while grade 3-4 stomatitis was observed in 17/20 patients (85%) and in 4/7 patients (57%), respectively. Total parenteral nutrition was required in all patients for a median of 9 days (range 0-23) both after the first and the second conditioning course. One patient experienced hemorrhagic cystitis due to the high dose cyclophosphamide.

Cardiac toxicity

Cardiac toxicity was severe and responsible for the only toxic death. Five out of 20 (25%) patients developed congestive heart failure (CHF). CHF occurred in 3 patients after the first course of HDCT, whereas for the remaining two patients CHF was documented after the second course, at 2 months in one case and at 10 months in the other. All but one of the patients who developed CHF received four courses of epirubicin.

Post-surgical treatment

Only 6 out of 19 patients received 50 Gy chest wall radiotherapy according to the protocol guidelines. Tamoxifen 30 mg/die for 2 years was given to 13 patients whose tumors were estrogen or progesterone receptor positive.

Discussion

Before the introduction of systemic chemotherapy, patients with IBC treated with surgery, radiation therapy or both had a very poor prognosis. With the development of combined modality treatment containing neoadjuvant chemotherapy a dramatic change occurred in the prognosis of IBC with objective response rates of nearly 80% and a 5-year survival rate of 50%.[9] In our series the Kaplan-Meier estimates of median DFS and OS were 54% and 63%, respectively, and the projected DFS and OS at 4 years were 58% and 74%, respectively. Such results compare favorably with the outcomes of large prospective series of patients treated with combined modality treatment alone.[5,10-12] Therefore, our data are consistent with those of other five larger series of patients affected by IBC and treated with high dose chemotherapy.[13-17] It is noteworthy that the DFS curves reported in the aforementioned series did not show a plateau, and neither did ours [Figure 2]. Longer follow-up is necessary to determine the real advantage of such an intensive treatment approach. Furthermore, these early encouraging outcomes may be related to the selection of patients with better prognostic characteristics. This concern has already reported for HDCT clinical trials involving women with non-IBC.[18] Comparisons between different series are always difficult because of differences in chemotherapy regimens, schedules, local treatment

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modalities, and staging systems. Only controlled randomized trials will be able to indicate the benefit of employing high dose chemotherapy in this setting, but because of the rarity of IBC, well-designed randomized trials to address this question may be difficult to carry out. Nevertheless, studies comparing conventional versus intensified treatment in locally advanced breast cancer are now ongoing and patients with IBC should be enrolled too.

The response to primary chemotherapy seems to be one of the most reliable prognostic factors,[3-5] although the question is still considered controversial by some.[10,19] The regimen we used proved to be very effective with a 95% overall response rate. In our series of patients, the achievement of a pathologic complete remission at surgery seemed to give a benefit in terms of disease-free survival that has not, however, yet reached a plateau. It is well established for primary breast cancer that the extent of axillary lymph node involvement is the most important prognostic factor. As far as IBC is concerned this statement is still to be proved even though already reported.[7] Half of our patients had negative axillary nodes at the time of surgery, which compares favorably with other published reports.[15,16] However, in our experience, the persistence of axillary involvement did not translate into a worse outcome. This unexpected observation may be the result of statistical sampling error, or due to cohort imbalance in other potential prognostic factors not examined in our study. The toxicity of our conditioning regimen was consistent with that of other previous reports except for the cardiac toxicity. In particular, the first course of HDCT resulted in an 85% rate of severe stomatitis. All patients received prophylaxis with mouthwashes containing amphotericin B and chlorhexidine. There are a few promising data on the role of GM-CSF in the prevention and treatment of oral mucositis in patients undergoing high-dose chemotherapy,[20,21] but definitive results are needed and one randomized trial is ongoing in our department to address this issue.

We observed a high rate of cardiac toxic events in our series and this complication was responsible for the only toxic death in the series. Five out of 20 patients (25%) developed CHF and of these four patients had received 4 courses of induction epirubicin; the last patient did not receive the fourth course because of our protocol amendment. None of the patients has reached the maximum tolerated cumulative dose of either epirubicin (900 mg/m^2)[22] or mitoxantrone (140 mg/m^2).[23] However, the cardiotoxicity of mitoxantrone is not always easily predictable. Vorobiof *et al*.[24] have previously described that a 10% or greater decrease in the LVEF occured at doses of 26-98 mg/m^2 in 6 out of 20 patients (30%). Bowers *et al*. have already reported a series of 44 patients with metastatic breast cancer treated with thiotepa (900 mg/m^2) and mitoxantrone administered using a dose escalation schedule. The dose-limiting non-hematologic toxicity of mitoxantrone was cardiac, the maximum tolerated dose being 50 mg/m^2.[25] Therefore, the cardiac toxicity of the anthracenedione might be dependent on peak dose as well as cumulative dose. This effect was probably enhanced in our study by the contemporary administration of high dose cyclophosphamide. In an attempt to decrease the cardiotoxicity of our treatment program we decided to eliminate the fourth course of induction epirubicin in the last four patients through a protocol amendment. In order to reduce the cardiotoxic risk further another suggestion is to administer no more than one course of high dose mitoxantrone, using an alternative high dose schedule such as CTCb[15] or melphalan and thiotepa, prolonging the time of infusion of epirubicin,[26] evaluating the role of cardioprotective agents such as dexrazoxane, and testing the importance of serum level of cardiac troponin-T with view to assessing the cardiac damage as early as possible.[27]

Few patients underwent the second course of HDCT: the main reason was an inadequate number of progenitor cells collected in 6 cases and non-hematologic toxicity after the first graft in the other 7 patients. A major clinical issue is to define the minimum number of cells necessary for rapid hematopoietic recovery after high-dose chemotherapy and some investigators have proposed 2 or 2.5×10^6 cells/kg/bw as the minimal threshold for rapid hematopoietic reconstitution.[28,29] Therefore, the target number of CD34$^+$ cells to be collected for each graft might have been excessively high in our study design.

At present many issues remain unresolved. These include the optimal combination of the conditioning regimen, optimal number of induction chemotherapy courses, whether maintenance therapy is needed, or surgery, radiation or both as local therapy. A large,multicenter, possibly randomized, study is warranted to address these issues. Most of all, the main focus of future studies should be to investigate new strategies to maintain the good results achieved by induction chemotherapy that allowed us to obtain a 95% overall response rate. In order to pursue this aim we need to find new non-cross-resistant regimens, and identify and correctly locate new biological strategies, such as the administration of antiangiogenic agents with the intent to prolong tumor dormancy and inhibit tumor growth, or the introduction of trastuzumab in patients with HER2 overexpression.

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Contributions and Acknowledgments

CD and AC share main responsibility for all aspects of this study and for writing the paper. GR, AT, AM, RS, MA, GLF and MM contributed to critical revision of the manuscript. BV was in charge of the data management. All authors: final approval of the definitive version.

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Disclosures

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Manuscript processing

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Potential implications for clinical practice

Dose-dense epirubicin followed by HDCT may obtain a high rate of objective responses.We have to reconsider the maximum tolerated cumulative dose of anthracycline and anthracenedione when we plan to administer these drugs at high doses and/or sequentially.

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