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Breast cancer

Multiple cycles of dose-intensive chemotherapy with repeated stem cell support as induction treatment in metastatic breast cancer: a feasibility study

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Summary:

The purpose of this trial was to study feasibility and tolerance of a dose-intensive multicyclic alternating induction chemotherapy with repeated stem cell support in a series of 43 metastatic breast cancer patients. Anthracycline-naive patients ($n = 21$) received cyclophosphamide 2.5 g/m^2 plus doxorubicin 80 mg/m^2 alternating every 14 days with paclitaxel 200–350 mg/m^2 plus cisplatin 120 mg/m^2. Patients who had previously received anthracyclines ($n = 22$) received cisplatin 120 mg/m^2 plus etoposide 600 mg/m^2 alternating with paclitaxel 200–350 mg/m^2 plus ifosfamide 8 g/m^2. Peripheral blood stem cells were infused after every course except the first, with a median CD34$^+$ dose of 2.1 × 10^6/kg per cycle. Positive selection of CD34$^+$ cells was performed in good mobilizers. The median number of cycles administered was six (4–8), and the time interval between them was 17 days. Median summation dose intensities (SDI) actually administered for the CA-TP and PE-TI protocol were 4.95 and 4.69, respectively (87% of scheduled SDI). There were 15 complete (35%) and 21 partial responses (49%), for an overall response rate of 84% (95% CI, 73%–95%). Infection or neutropenic fever occurred in 50% of the cycles. There was one treatment-related death. After a median follow-up of 26 months, the median event-free-survival was 12 months (95% CI: 10–14) and overall survival was 31 months. These high dose-intensity induction treatments seem to be feasible with sequential stem cell support. *Bone Marrow Transplantation* (2001) **28,** 235–242.

Keywords: dose-intensity; breast cancer; peripheral blood stem cells; positive selection

The dose–response relationship in breast cancer (BC) therapy has been a matter of controversy for the last two decades. Extensive literature reviews by Hryniuk *et al*[1,2] have found dose intensity to be correlated with response rate and survival. This effect has been considered in the rationale of many clinical trials that attempted to improve long-term survival in metastatic BC by delivering single courses of high-dose chemotherapy (HDC). Despite some promising data derived from phase II trials, results of the randomized studies published thus far have failed to show a sound clinical benefit for single autografts.[3–5]

There might be other ways to take advantage of the dose-intensity principle. *In vitro*, repeated doses of chemotherapy cause more cell kill than single doses, even though the total amount of drug administered is the same.[6] The classical model of Gompertzian kinetics provides a possible explanation for this fact through rapid compensatory re-growth of the resistant clones not eradicated by HDC.[7] The spread of the cytotoxic effect over a longer period of time might increase cell kill and reduce the probability of drug resistance.[8] Multicyclic treatment schemes appear to take advantage of the inherent time-dependant responsiveness of most cancer tissues.

Autologous peripheral blood stem cell infusions have been extensively used to support single courses of HDC. Nonetheless, their possible use in programs of multicyclic non-myeloablative dose-intense chemotherapy has been little explored.[9–12] In November 1995, the Department of Oncology of University of Navarra, Spain, initiated a feasibility study that included a biweekly, alternating, dose-intensive chemotherapy regimen. The results observed in the first 43 patients with metastatic BC are presented in this report.

Materials and methods

Women with histologically proven metastatic BC were evaluated for study entry. An ECOG performance status of 0–1, age less than 65 years, and no evidence of cardiac, pulmonary, liver or renal impairment were required. All patients gave written informed consent according to institutional policy before entering the study. Patients presenting with brain metastases, leptomeningeal disease, or bone marrow involvement, as well as patients previously

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Table 1 Chemotherapy regimen

	Prior anthracyclines: PE-TI protocol	*No prior anthracyclines: CA-TP protocol*
Cycle A:	Cisplatin 120 mg/m^2 + Etoposide 600 mg/m^2	Cyclophosphamide 2.5 g/m^2 + Doxorubicin 80 mg/m^2
Cycle B:	Paclitaxel 200–340 mg/m^{2a} + Ifosfamide 8 g/m^2	Paclitaxel 200–350 mg/m^{2a} + Cisplatin 120 mg/m^2

[a]See text for dose-escalating strategy.

treated with chemotherapy for metastatic disease (including anthracycline-containing regimens and HDC) were not excluded.

Pretreatment assessment included medical history and physical examination, chest-X-ray, thoraco-abdominal CT scan, bone scan, brain MRI, EKG, LVEF, respiratory function tests, metabolic panel, serum tumor markers (CA15.3 and CEA), and HIV, CMV, HbsAg, HVC titers. A positron emission tomography (PET) with 18-fluorodeoxiglucose was performed before treatment in some cases. Bone marrow biopsy and aspiration were performed in the presence of multiple bone metastasis and/or peripheral cytopenia.

Treatment

A double-lumen Hickman central catheter was placed before the start of treatment. The chemotherapy regimen and treatment schedule are shown in Table 1 and Figure 1. Treatment included six or eight alternating cycles with a scheduled interval of 14 days between treatments. The interval was lengthened if the platelet count was below 40 $\times$ 10^9/l or if there was an unresolved WHO grade 3 or 4 non-hematological toxicity, but dose reductions were not scheduled. Patients were divided into two groups according to prior treatment with anthracyclines (Table 1).

Group 1: Twenty-two patients with prior anthracycline-based chemotherapy were treated according to the PE-TI protocol. This protocol consisted of cisplatin 30 mg/m^2 i.v. twice daily on days 1 and 2 (total dose: 120 mg/m^2) plus etoposide 150 mg/m^2 i.v. twice daily on days 1 and 2 (total dose: 600 mg/m^2 i.v.) (cycle A), alternating every 2 weeks with paclitaxel 200–350 mg/m^2 i.v. (see text below) once daily on day 1 plus ifosfamide 2 g/m^2 i.v. twice daily on days 1 and 2 (total dose: 8 g/m^2) (cycle B). Paclitaxel premedication included dexamethasone, cimetidine, and diphenhydramine. Ifosfamide was administered with hyperhydration and 2-mercapto-ethane sulfonate (Mesna) uroprotection.

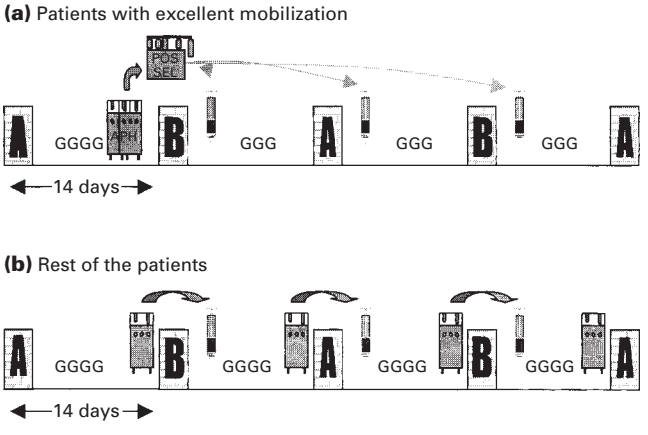

Figure 1 Treatment schedule. Cells were reinfused 48 h after chemotherapy except after the first cycle (syringes in the diagram). A = cycle A; B = cycle B; G = G-CSF; APH = leukapheresis; POS SEL = positive selection.

Group 2: Twenty-one anthracycline-naive patients were treated according to the CA-TP protocol. This protocol included cyclophosphamide 625 mg/m^2 i.v. twice daily on days 1 and 2 (total dose: 2.5 g/m^2) plus doxorubicin 20 mg/m^2 i.v. twice daily on days 1 and 2 (total dose: 80 mg/m^2) (cycle A), alternating with paclitaxel 200–350 mg/m^2 (see text below) i.v. on day 1 plus cisplatin 30 mg/m^2 i.v. twice daily on days 1 and 2 (total dose: 120 mg/m^2) (cycle B). Cyclophosphamide was administered with hyperhydration and Mesna uroprotection.

Ondansetron, ACTH, and metoclopramide with lorazepam were given to control emesis. Patients received escalating doses of paclitaxel (without intrapatient dose escalation). The first 12 patients received 200 mg/m^2; the next five patients 250 mg/m^2; nine patients received 300 mg/m^2, and the 17 last patients received 350 mg/m^2. Finally, the maximum tolerated dose was established at 300 mg/m^2 (see below).

Hematopoietic support

The stem cells were mobilized with G-CSF, 5–12 μg/kg/day subcutaneously beginning on day 9. Peripheral blood CD34 cell counts were performed daily from day 13. The optimal day for cell collection was decided on an individual basis, considering CD34, leukocyte, and platelet counts. Collections were performed with continuous flow apheresis machines (Cobe Spectra; Cobe BCT, Barcelona, Spain) or CS3000plus (Baxter, Barcelona, Spain), processing two to five blood volumes. The first 18 patients were mobilized after every course. A single leukapheresis was performed in each mobilization, and the whole apheresis product was infused after the next course. The rationale for this was two-fold: first, to avoid collection of contaminating tumor cells through an '*in vivo* purging' effect in this population of patients with active metastatic disease not in remission;[13] second, to procure high doses of stem cells to minimize hematopoietic damage. In February 1997, an interim analysis showed that a dosage between 2 and 4 $\times$ 10^6/kg CD34 cells was optimal.[14] From this point, patients undergoing excellent mobilizations (peak CD34$^+$ cells in peripheral blood greater than 90 cells/mm^3) were considered for positive selection of CD34$^+$ cells. In this case, two to three consecutive leukaphereses were performed, and cells were selected with an Isolex 300i (Baxter) device according to manufacturer's recommended procedures. The positive fraction was divided for the support of as many courses as possible, with the goal of delivering approximately 2 $\times$ 10^6/kg CD34$^+$ cells per cycle. Patients

with less than excellent mobilizations were repetitively mobilized in every cycle as stated above (Figure 1).

Cellular products were infused 48 h after the end of every chemotherapy course. G-CSF 5 μg/kg/day subcutaneously was administered from days 6 to 10 to promote granulocyte recovery, even if it was not necessary to mobilize the patient. The first course of the program was given without cellular support.

Dose-intensity calculation

Dose intensity (DI) is the amount of drug delivered per unit time in weeks. This parameter, first introduced by Hryniuk and Bush[1] in 1984, has been used to test the dose–response relationship in different malignancies, as well as to compare different chemotherapy regimens. A new parameter, summation dose intensity (SDI), integrates the contribution of each individual agent within a combination regimen[2] and shows a stronger correlation with favorable outcome than the classical DI parameter. The SDI calculations are shown in Table 2. The planned SDI of the CA-TP combination protocol was 5.42 SDI units, based on a 14-day treatment schedule and considering the finally recommended dose of 300 mg/m^2 of paclitaxel. The planned SDI of PE-TI combination was 5.16 SDI units. We assigned to ifosfamide the dose-intensity value of 1111 mg/m^2/week of cyclophosphamide, extrapolating the equivalence between these two drugs.[15]

Response assessment

Clinical and radiologic tumor response was evaluated according to the International Union Against Cancer (UICC) criteria.[16] In addition, serum chemistries and serum markers were conducted biweekly before every cycle. Response was assessed every two courses till the end of the program by the same imaging technique as used at baseline. Patients in complete response after six cycles of chemotherapy were evaluated for consolidation therapy as outlined below. Patients not achieving complete response after six cycles received two additional cycles of chemotherapy.

In patients with bone metastasis, partial response was defined as pain relief along with stable or improved bone scan findings and complete or near complete normalization of serum markers at the completion of therapy. Complete response was defined as complete normalization of bone scan. When evaluation of residual lesions on CT scan was difficult, abdominal MRI (in the case of liver metastasis) or PET were performed.

Table 2 Dose intensity calculations

Regimen[a]	*RDI* (mg/m^2/week)	*UDI* (mg/m^2/week)	*SDI*
CA-TP			
Cyclophosphamide	625	650	625/650 = 0.96
Doxorubicin	20	12.5	20/12.5 = 1.6
Paclitaxel	75	50	75/50 = 1.5
Cisplatin	30	22	30/22 = 1.36
Total SDI			5.42 UDIs
PE-TI			
Paclitaxel	75	50	75/50 = 1.5
Ifosfamide	1111[b]	650[c]	1111/650 = 1.70
Cisplatin	30	22	30/22 = 1.36
Etoposide	150	640	150/640 = 0.44
Total SDI			5.16 UDIs

RDI = relative dose-intensity in mg/m^2/per week; UDI = unit of dose-intensity. Dose-intensity required to produce a 30% complete response plus partial response (CR+PR) rate when this agent is used alone; SDI = summation dose-intensity.
Dose-intensity calculations according to Hryniuk *et al*.[2] Paclitaxel dose-intensity has been calculated according to the finally recommended dose of 300 mg/m^2.
[a]Alternating biweekly cycles. Note that the interval between doses of the same drug is 4 weeks.
[b]1111 mg/m^2/wk = the equivalent dose of cyclophosphamide from 2 g/m^2/week of ifosfamide.[20]
[c]650 = 1 UDI of cyclophosphamide.

Toxicity evaluation and supportive care

Organ-system toxicity was graded according to the criteria of Petersen *et al*[17] for intensive chemotherapy with stem cell transplantation. If the toxicity found in these series had been graded according to the World Health Organization system,[18] all patients would have experienced grade 4 hematological toxicity and grade 3 and 4 toxicities in several organs. Emesis and hematologic toxicity were evaluated according to the WHO criteria[18] because Petersen's criteria were not applicable.

Patients were managed on an outpatient basis between treatments. Patients with febrile granulocytopenia, documented infections, or non-infectious complications were hospitalized. Patients received transfusions of packed red blood cells if the hemoglobin level was less than 9 g/dl and a single donor apheresis unit of platelets when the platelet count was less than 10×10^9/l. All the hemoderivates underwent prior filtration for leukocyte depletion.

Consolidation therapy

Consolidation treatment was decided on an individual basis, taking into account the extent of initial disease and the response obtained at the completion of the sequential intensive chemotherapy regimen (SICT). All patients with areas of initial bulky disease were evaluated for radiation therapy. HDC with stem cell support and adjuvant hormonal therapy or adoptive immunotherapy were offered to responding patients after SICT.

Statistics

Descriptive data are given as median values, with the range in parenthesis. Event-free survival was calculated from the first day of the SICT regimen until the appearance of disease progression or death. Overall survival was calculated from the first day of the SICT regimen until the date of death or the last follow-up. Both survival curves were calculated with the Kaplan–Meier method and compared with the log-rank test. Categorical variables (ie different characteristics in responding patients) were compared with the Chi-square method. Kolmogorov–Smirnov test with Lilliefor's adjustment was used to test the normal distribution.

The Spearman rank correlation test was used to explore the relationship between $CD34^+$ cell dosage and treatment delay and also the correlation between $CD34^+$ cell counts and the cycle used for mobilization (ordinal variable with seven categories). Comparisons between two groups of non-normally distributed variables (delay in patients receiving CA-TP or PE-TI protocols; delay in patients having received or not previous stem cell transplantation) were made with the Mann–Whitney test. For comparisons among multiple groups (delay in patients receiving 0 to four previous chemotherapy lines), the Kruskall–Wallis test was used. Both database management and statistical calculations were done with the SPSS 7.5 package.

Results

Patients

Forty-three females with metastatic BC participated in this study between November 1995 and February 1998. Results are available for 43 patients. A heavy disease burden characterized the patient profile in most of the cases. Pretreatment characteristics are specified in Table 3.

Dose-intensity

Forty-three patients completed the treatment plan as scheduled. The median number of cycles administered was six (range, 4–8), and the median time interval between cycles was 17 days. The overall median SDI actually administered in the CA-TP protocol was 4.95 SDI units, which represents a mean of 87.4% of the planned SDI. The overall SDI given of the PE-TI protocol was 4.69 SDI units, representing a mean of 86.7% of the planned SDI. These calculations were done on a patient-by-patient basis, considering the dose of paclitaxel assigned to each one.

Results in cellular support

A total of 154 mobilizations were performed. The median peak $CD34^+$ count in peripheral blood was 33×10^6/l cells (range, 1.4–940). In patients repeatedly mobilized, the intensity of the mobilization response progressively declined along the treatment (Figures 2 and 3). Both the peak peripheral blood $CD34^+$ count and the number of $CD34^+$ cells collected in a single apheresis showed a significant inverse rank correlation with the ordinal number of the cycle used for mobilization ($R_s = -0.48$ and $P < 0.0005$ in both cases). The median dose of $CD34^+$ cells infused per cycle was 2.1×10^6/kg (range, 0.1–91). Since the positive selection procedure was available, 25 patients entered the SICT program and 14 of these underwent positive selection following our eligibility criteria (sufficient mobilization to make likely the support of several courses with the positive fraction from a single selection). The positive fraction could be distributed for the support of a median of four courses (range, 2–6), with a median $CD34^+$ dose per cycle of 1.8×10^6/kg (range, 0.9–2.5). Among patients not undergoing positive selection, a median of five mobilizations per patient were performed.

The median delay for the administration of the next course over the scheduled interval of 2 weeks was 3 days (range, 0–35), in most cases due to delay in reaching hematopoietic recovery or optimal mobilization. There was a non-linear relationship with a significant inverse correlation between $CD34^+$ cell dose infused and the delay for the administration of the next course ($R_s = -0.29$; $P < 0.001$)

Table 3 Pretreatment characteristics of patients

Characteristic	*Number*	*Percent*
Size of patient population	43	
Age, median (range)	44 (23–61)	
Performance status (ECOG) (range)	0 (0–1)	
Previous adjuvant chemotherapy	32/43	74
Number of prior CT lines, median (range)	2 (0–5)	
Prior CT for metastatic disease	17/43	39
Number of prior CT lines for metastasis, median (range)	1 (1–4)	
Previous anthracyclines	22/43	51
Previous HDC[a]	12/43	28
Adjuvant setting	5/12	
Metastatic setting	7/12	
Number of metastatic sites[b]		
1	18/43	41
>1	25/43	59
Sites of metastases:		
Breast +/– locoregional relapse	7/43	16
Distant lymph node metastases	7/43	16
Lung/Pleura	15/43	35
Liver	15/43	35
Bone/bone marrow	29/43	67
CNS/Leptomeningeal	7/43	16

CT = chemotherapy; HDC = high-dose chemotherapy.
[a]HDC had already been for metastatic disease in seven patients.
[b]See Table 4 for details on sites of disease.

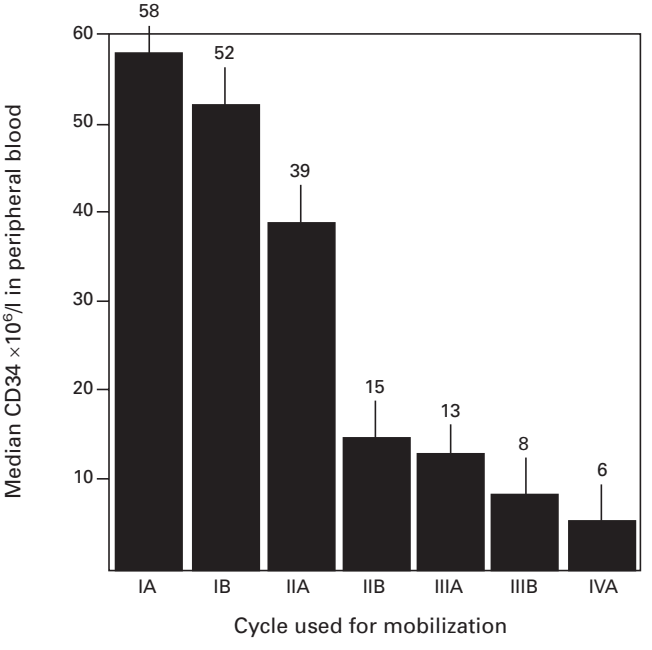

Figure 2 Median peak peripheral blood $CD34^+$ cell count achieved according to the cycle used for mobilization. Only results from patients repeatedly mobilized are included (see text).

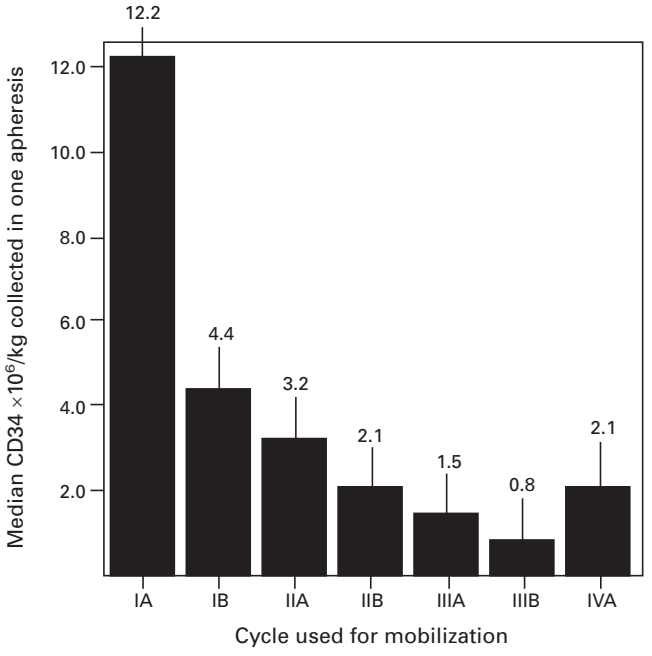

Figure 3 Median number of CD34+ cells collected in a single apheresis according to the cycle used for mobilization. Only results from patients repeatedly mobilized are included (see text).

in the courses supported with non-selected aphereses products (see Figure 4). This correlation was not significant if only positive fraction-supported cycles were considered (R_s = –0.019; P = 0.93). The delay for the next cycle was not significantly related to the type of SICT administered (CA-TP or PE-TI), the number of chemotherapy lines received prior to the SICT, the previous treatment with stem cell transplantation, or the type of cellular product used for hematopoietic support (unselected apheresis product or positive fraction).

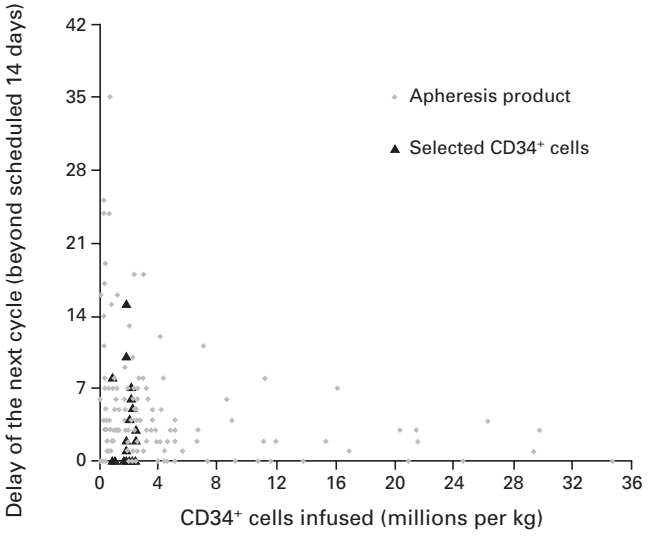

Figure 4 Relationship between the CD34+ cell dose infused after one cycle and the delay for the administration of the following one. The last course of each patient has been excluded from this analysis.

Responses

Forty-three patients were evaluable for response. There were 15 (35%) complete responses, 21 (49%) partial responses, two (5%) patients with stable disease and five (12%) progressions, for an overall response rate of 84% (95% confidence interval, 73%–95%). All non-responding patients had extensive disease, with more than two sites of metastasis, including CNS in three cases. Among eight patients presenting central nervous system metastasis (with other organs affected in six), there were two complete and one partial response. Of interest, the overall response rate for liver metastasis was 80%. There was no significant difference in response rate between CA-TP (seven complete and 11 partial, among 21 patients) and PE-TI treated patients (eight complete and 10 partial among 22).

Toxicity

Times to neutrophil and platelet recovery are not reported, as full blood counts were not performed on a daily basis, except when patients were hospitalized due to complications. The median delay between cycles (see data above) and hemoderivate requirement have been used to estimate hematologic toxicity. A median of 3.5 (range, 0–49) platelet transfusions per patient and 16.5 (range, 4–35) units of red blood cells per patient were required.

Neutropenic fever occurred in 50% of the cycles. Positive blood cultures were reported in 14 patients (32%), excluding blood cultures positive for *Staphylococcus epidermidis*.

Organ system toxicities are summarized in Table 4. Two patients developed acute renal failure and required renal dialysis, and one patient developed paralytic ileus and required nasogastric aspiration. One patient developed grade II cardiotoxicity with a decrease of the left ventricular ejection fraction down to 30%. There was no ifosfamide-related hemorrhagic cystitis or severe encephalopathy. Nine patients developed WHO grade 3 nausea/vomiting, but this never hampered the delivery of the treatment program. Generalized fatigue was present in all patients and was cumulative. Seven patients experienced mild transient bradycardia.

Three cases of acute reversible encephalopathy, probably

Table 4 Toxicity

	Grade II	*Grade III*
Cardiac	1	0
Bladder	0	0
Renal	2	2
Pulmonary	0	0
Hepatic	1	0
CNS	0	0
Stomatitis	2	0
Gastrointestinal	1	1

CNS = central nervous system.
Toxicity according to Peterson *et al* criteria.[18]
Note: Grade I toxicity is defined as mild symptoms always reversible without treatment (similar to WHO grade I toxicities). Data not reported. Grade IV regimen-related toxicity is defined as fatal toxicity.

associated with paclitaxel,[19] were observed at the 350 mg/m^2 dose. These patients developed severe hypotension and loss of consciousness that was reversible and non-fatal in all cases. After these events, we concluded that the maximum tolerated dose of paclitaxel for these programs was 300 mg/m^2.

There was one treatment-related death due to multiorganic failure of probable septic origin. CT scan documented progression of disease.

Consolidation therapy

Patients received different modalities of consolidation therapy, depending on the response observed. After the completion of chemotherapy, 19 patients received irradiation to sites of initial bulky disease or residual lesions that had responded to chemotherapy. Three patients achieving complete response received a single course of HDC as consolidation. Nine responding patients entered a program of adoptive immunotherapy, and six patients received hormonotherapy. Eight patients did not receive any type of consolidation therapy.

Outcome

After a median follow-up of 26 months (range, 16–44), median event-free survival was 12 months (95% CI, 10–14) (Figure 5). The 3-year overall survival rate was 43%, with a median survival time of 31 months (Figure 6).

Median time to progression was 13 months (95% CI, 11–15). At the time of this analysis, 18 patients (41%) have died of disease. Twenty-three patients (53%) are still alive, seven of them (16%) with no evidence of disease. Two patients in complete response died without evidence of disease, due to heart failure and sudden death of unknown origin, respectively.

Five of the seven patients alive with no evidence of disease obtained complete remision (CR) with the SICT and were subsequently irradiated. The other two patients obtained partial remision (PR) after SICT and received radiotherapy as consolidation on the remaining hepatic lesions; they have remained disease-free for over 20 months of follow-up. Sixteen patients are alive with disease, and some of them have received further chemotherapy or hormonal therapy after SICT.

We found no statistically significant differences in event-free survival or overall survival among CATP- and PETI-treated patients, among patients who achieved complete response and those who did not, among patients previously treated with chemotherapy and chemotherapy-naive patients, among patients previously treated with HDC or not, or among patients receiving different doses of paclitaxel.

Sites of relapse after SICT

Median duration of response was 12 months (95% CI, 11–28). Recurrences have been observed predominantly in areas with previous bulky disease (75% of cases). Eight of 31 (25%) patients have relapsed in areas that were not involved initially, five of them with new onset brain metastasis. Fourteen of the 19 patients who were irradiated are still alive with no evidence of disease progression in the areas treated with irradiation.

Discussion

The patients in this study received multiple cycles of chemotherapy with higher than conventional, but far from myeloablative, doses of several drugs at short time intervals. An alternating schedule was chosen in order to allow the early introduction of as many active non-cross-resistant drugs as possible. Although any of the chemotherapy courses used in this protocol might have been safely administered without any hematopoietic support, its quick repetition within a 2-week interval would have probably lead to cumulative marrow toxicity. Thus, we expected this regimen to be tolerated with strong hematopoietic support with both PBSC and G-CSF. The chemotherapy schedule was discontinued in only one patient due to cardiotoxicity. Median interval between cycles was 17 days, only 3 days more than the planned biweekly interval. The adminis-

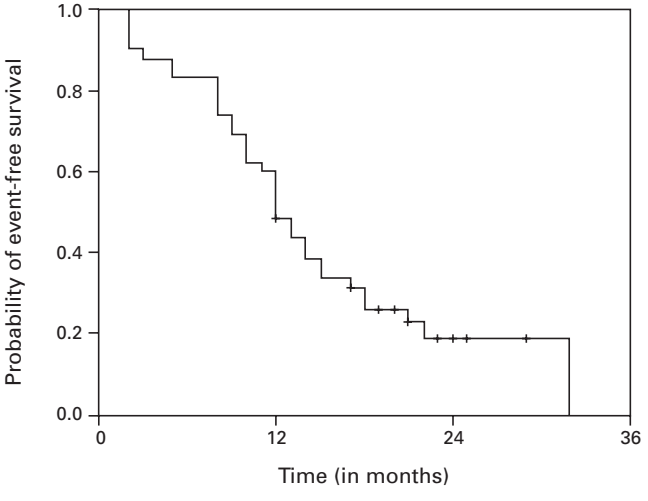

Figure 5 Overall survival.

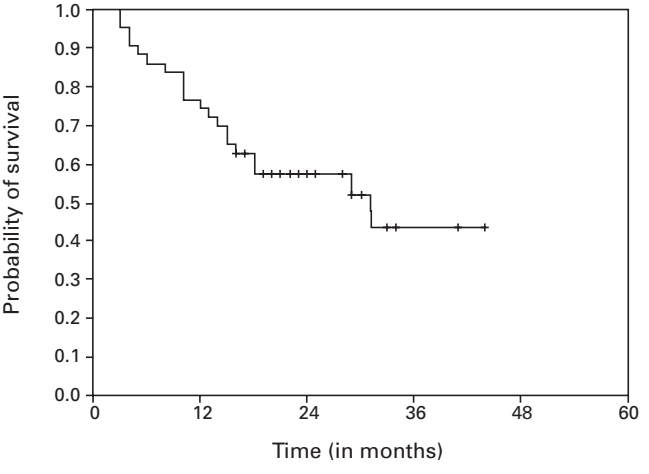

Figure 6 Event-free survival.

tration of this dose-intensive regimen with repeated stem cell support seems to be feasible. We had also come to the same conclusion after testing this protocol in advanced ovarian carcinoma and Ewing's sarcoma.[20,21] Previous reports have shown the feasibility of different multicyclic dose-intensive regimens with stem cell support.[9–12]

The dose of $CD34^+$ cells administered inversely correlated with the delay over the scheduled 2-week interval between cycles. In a multivariate analysis, we found the $CD34^+$ cell dose to be a significant predictor of the actual administered dose intensity.[22] Nevertheless, above certain threshold values of cells, further increases in the CD34 dose may not lead to further significant decreases in the interval.[14,22] A similar effect has been described in single autografts with stem cell support, where recoveries are never reached before certain points (8 to 9 days post infusion), regardless of the $CD34^+$ cell dose administered.[23] Moreover, in our program, an interval shorter than 2 weeks was not intended. These are reasonable explanations for the lack of correlation between $CD34^+$ cell dose and delay in the group supported with positive fraction, where the $CD34^+$ cell dose was planned prior to cryopreservation.

Contamination of the graft by malignant cells is a common occurrence in metastatic breast cancer.[24–27] Most of the experience in this area is based on the study of apheresis products collected when patients who have responded to previous induction chemotherapy are about to be intensified. The patients in our series were mobilized during the recovery from induction cycles, when active metastatic disease was still present and the risk of contamination would theoretically be higher. Although the actual prognostic significance of contaminating tumor cells remains controversial,[24–27] we considered it appropriate to infuse an unselected cellular product immediately after the next one or two courses following collection, but not at a later time, when the tumor burden could have been markedly reduced by the treatment. In most of our patients, enough progenitors to support the whole SICT program could have been collected with a short series of leukaphereses in a single mobilization. Nevertheless, we only performed this procedure when positive selection of $CD34^+$ cells was possible. Hematopoietic support with selected products was associated with an excellent observance of the dose intensity plan, with a median delay of 1.5 days in this group. The distribution of the positive fraction from a single selection for the support of several courses contributes to the economical feasibility of this program. On the other hand, patients not undergoing cellular selection were mobilized repetitively after each cycle, in an attempt to perform '*in vivo* purging' of the products.[11,13] We could mobilize the patients up to seven times without relevant compromise in the dose intensity.

HDC with stem cell support has been widely used as consolidation treatment after induction with conventional-dose chemotherapy. Alternatively, the aim of our protocol was to test a high dose-intensity protocol as induction treatment. We used the SDI method for the DI calculations.[2] Hryniuk *et al* have reported a 30% increase in the overall response rates in metastatic BC by SDI increases of one unit. Of note, according to Hryniuk's literature review, none of the comparative trials testing dose intensity in conventional chemotherapy for metastric BC has targeted a sufficient difference in SDI among arms (1.5 units) to expect a meaningful increase in CR rate (15%) or in median survival time (6 months). The maximum SDI reached by a CMF combination in a controlled trial is 1.98.[28] By administering GM-CSF, Ardizzoni *et al*[29] escalated the SDI of the FEC regimen up to 2.11 units. The projected SDI of our CA-TP and PE-TI regimens for the recommended dose of paclitaxel are 5.42 and 5.16, respectively, higher than that of any multicyclic chemotherapy tested in randomized trial for first-line treatment of metastatic BC. Moreover, the mean dose intensity actually administered in our series was above 85% for both regimens, showing that these levels of dose intensity are a realistic goal.

We found that consolidation treatment has probably been of benefit in our series. Fourteen of 19 patients who were irradiated after SICT are alive without evidence of progression at last follow-up. In addition, the seven patients who remain alive without evidence of disease after a median follow-up of 25 months received irradiation over predominant sites of disease after obtaining complete or partial response. In our series, 75% of the areas that showed a subsequent recurrence (or regrowth of persistent disease after chemotherapy) had been initially involved. Carter *et al*[30] reported how the addition of radiation to HDC appeared to reduce the failure rate at initial sites of disease (28% without consolidation radiotherapy *vs* 62% with it) and improve event-free survival (21% *vs* 31%) and overall survival (16% *vs* 30%).

Most patients have received further chemotherapy after disease progression was documented. This circumstance should be borne in mind on interpreting the overall survival results of our series. Docetaxel and/or vinorelbine have been the most frequently used drugs. In general, hematological tolerance has been good despite previous SICT, without prolonged delays between subsequent cycles.

In this series, a strong hematopoietic support made feasible a multicyclic chemotherapy program with substantially high-dose intensity. The response results achieved in a scarcely selected population warrant further comparison with other therapeutic approaches for advanced BC.

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