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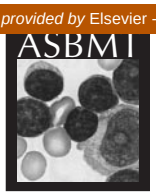

The Impact of Induction Duration and the Number of High-Dose Cycles on the Long-term Survival of Women with Metastatic Breast Cancer Treated with High-Dose Chemotherapy with Stem Cell Rescue: An Analysis of Sequential Phase I/II Trials from the Dana-Farber/ Beth Israel STAMP Program

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ABSTRACT

Although high-dose chemotherapy (HDC) with stem cell rescue for the treatment of women with metastatic breast cancer (MBC) is currently a controversial strategy, we report the long-term outcomes of women undergoing high-dose therapy for MBC over the past 12 years while participating in a sequence of research studies transitioning between a single to a double intensification approach. Univariate and multivariate analyses provide a framework to understand the prognostic factors important for event-free and overall survival. Between May 1988 and April 1998, we enrolled 188 women with MBC into 3 trials of previously reported sequential transplantation strategies. Trial I (long induction/single transplantation) accepted 62 women in partial or complete response to an unspecified induction therapy and treated them with high-dose CTCb (cyclophosphamide, thiotepa, and carboplatin) supported by marrow or peripheral blood progenitor cells (PBPC). Trial II (long induction/double transplantation) accepted 68 women in partial or complete response to an unspecified induction therapy, and mobilized stem cells with 2 cycles of AF (doxorubicin and 5-fluorouracil) with granulocyte colony-stimulating factor (G-CSF). These women then received 1 cycle of high-dose single-agent melphalan followed 3 to 5 weeks later by CTCb, each with marrow or PBPC support. Trial III (short induction/double transplantation) enrolled 58 women prior to chemotherapy treatment for metastatic disease. Induction/mobilization consisted of 2 cycles given 14 days apart of doxorubicin and G-CSF. In contrast to trials I and II, patients with stable disease or better response to induction were eligible to proceed ahead with 2 cycles of HDC, 1 being CTCb and the other being dose escalated paclitaxel together with high-dose melphalan (TxM). These 2 HDC regimens were administered 5 weeks apart. TxM was given first in 32 patients and CTCb was given first in 26 patients. The median follow-up periods for trials I, II, and III were 98, 62, and 39 months from the initiation of induction chemotherapy and 92, 55, and 36 months from last high-dose therapy, respectively. The patient characteristics upon entry into these trials were similar. Important differences were that only those patients achieving a partial response or better to induction therapy were enrolled and analyzed for trials I and II, but all patients were analyzed on an intent-to-treat basis for trial III, including those who did not receive intensification. The median event-free survival (EFS) times from induction chemotherapy were 13, 19, and 27 months for trials I, II, and III, respectively (III versus I + II, $P = .0004$; III versus I, $P = .0005$; III versus II, $P = .005$; II versus I, $P = .25$). The median overall survival (OS) times from induction chemotherapy were 30, 29, and 57 months for trials I, II, and III, respectively (III versus I + II, $P = .002$; III versus I, $P = .003$; III versus II, $P = .009$; II versus I, $P = .47$). By multivariate Cox regression, participation in the short induction/double transplantation trial III and having no prior adjuvant chemotherapy remained favorable prognostic factors for both EFS and OS. The presence of visceral

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disease shortened EFS, and hormone sensitivity was of borderline significance. No substantive differences in the characteristics of the patient populations between the 3 trials appeared to interact with outcomes. In conclusion, we found that single transplantation in responding patients after long induction achieves a small cohort of long-term survivors, similar to the results reported by other transplantation centers. Adding a cycle of single-agent high-dose melphalan in this context delayed median time to relapse but did not affect long-term EFS or OS. The double transplantation approach using CTCb and TxM early in the course of treatment was associated with the best EFS and overall survival and was safe, feasible, and tolerable. Treatment duration was only 14 weeks, and this treatment option eliminated lengthy induction chemotherapy. Although selection biases may have in part contributed to this effect, a randomized comparison of standard therapy versus short induction/double transplantation is warranted.

KEY WORDS

Metastatic breast cancer • Hematopoietic stem cell support • Double transplantation

INTRODUCTION

Patients with metastatic breast cancer (MBC) are considered incurable with conventional therapy. Palliation may be achieved in that combination chemotherapy regimens, especially those containing doxorubicin and/or taxanes, result in response rates of 50% to 80% and complete response rates of 4% to 27% in previously untreated patients [1]. Median response duration is generally less than 1 year. For example, in a recent randomized study reported by Sledge et al., the median time to treatment failure was 6 months for single-agent doxorubicin and paclitaxel and 8 months for the combination [2]. Overall median survival times were 19 to 22 months, with estrogen receptor negativity, visceral dominant disease, 3 or more sites of metastatic disease, and a short disease-free interval or prior adjuvant therapy being factors indicating poor prognosis [2]. Patients who are receiving conventional doxorubicin-containing chemotherapy but meet selection criteria for candidacy for high-dose therapy generally have a better prognosis [3-5]. In the MD Anderson experience, albeit with a high proportion of chemonaive and hormone receptor–positive patients, the median progression-free and overall survival times for this group of patients with metastatic disease were 16 and 30 months, and the 2- and 5-year progression-free survival rates were 31% and 7%, respectively [3].

High-dose therapy with hematopoietic stem cell support does increase complete response (CR) and near-complete response (nCR) rates compared with response rates expected after conventional chemotherapy alone [6]. The typical approach to high-dose therapy has been to treat patients with conventional-dose chemotherapy to a best response (long induction) and then to select the patients with responsive tumors for consolidation with a single cycle of high-dose chemotherapy (HDC). With this approach, approximately 50% of women with MBC responding to induction chemotherapy achieve a CR and/or nCR and approximately 15% to 20% remain in continuous CR at 5 years [7,8]. These results are remarkably consistent across many single and multi-institutional trials. This strategy is limited by the fact that only 70% of patients will have a sufficient response to be candidates and that most treated patients still relapse within 2 years. Given the acknowledged selection biases inherent in transplantation studies, it remains a matter of debate whether a single high-dose cycle is better than conventional therapy. In trial I, we report our updated long-term experience with this approach.

Nonetheless, the strong scientific pharmacologic basis for dose strategies, the observed high complete response rates, and the frequent association in cancer treatment between the development of high rates of CR and subsequent development of curative therapy support further investigation in this arena. One such direction, rendered potentially feasible by the increasing safety of high-dose therapy, is to deliver multiple-cycle HDC. Multiple cycles may enhance first-order cytotoxicity, particularly for BC, with its lower growth fraction. Moreover, more agents and higher cumulative doses may be delivered, potentially to overcome drug-resistant subpopulations [9-12]. In addition to cytokinetic issues, the solid tumor microenvironment is known to be dynamic, including features such as intermittent ischemia and hypoxia that would represent transient pharmacologic sanctuaries that may not be present with repeated cycles of therapy. Evidence from some models of double transplantation in mice indicates that tandem transplantation is more effective than a single transplantation [8]. Both trials II and III develop the double transplantation concept and demonstrate its feasibility.

Another concept deserving of investigation was the role of the induction therapy, the conventional dose therapy given to maximum response prior to high-dose therapy. Induction therapy prior to high-dose intensification has a number of possible advantages. These include reduction in tumor burden, reduction in stem cell contamination, and demonstration of chemotherapy sensitivity of the tumor. Thus patients with inadequately sensitive tumors could be spared the morbidity of HDC. Potential disadvantages to induction therapy include proliferation or induction of drug-resistant tumor populations and cumulative toxicities to the host and to stem cells. Several lines of preclinical evidence highlight the importance of acute acquired drug resistance [10-13] and the up-regulation of normal pathways responsive to cellular stress and damage [14-18]. In the clinic, repeated administration of the same agents produces most of the measurable effect by 4 cycles [19-22]. In general, 4 to 6 cycles of chemotherapy (no more or less) maximize curative outcomes, although maintenance chemotherapy is associated with increased duration of response. Moreover, induction therapy for BC typically achieves only a partial response, which corresponds to a median of about 1 log of cytoreduction in the face of almost 11 logs of tumor cells in metastatic disease.

We hypothesized that chemotherapy intensification late in the course of treatment (eg, after a median of 4-6 cycles)

Table 1. *Sequence of Studies: Schemas*

Study	N	Initial Therapy	HDC No. 1	HDC No. 2	Year
I	62	AFM × 4	CTCb		1988-1991
II	68	4 cycles→AF × 2	M	CTCb	1991-1994
III	32	A × 2	TxM	CTCb	1994-1996
	26	A × 2	CTCb	TxM	1996-1998

may not be as effective as early intensification. Based on these considerations, the design of the double transplantation/short induction trial (trial III) brought the high-dose intensifications within the first 4 cycles of chemotherapy and explored the sequence of the 2 transplantation regimens [8-11,23,24]. We now report the long-term outcomes of high-dose therapy for MBC at our institutions over the last 12 years and summarize by multivariate statistical analysis the prognostic factors that contribute to these outcomes.

METHODS

Eligibility for Protocols

Eligibility criteria for each study were described previously, but in general were similar across the trials [7,23-26]. Women with histologically documented MBC were eligible. No active central nervous system or histologic marrow involvement was allowed. The patients had to be physiologically under age 60 with a Zubrod performance status of 0 to 1. Prior adjuvant therapy was allowed. A disease-free interval (DFI) from completion of adjuvant chemotherapy to diagnosis of metastases or recurrence of at least 6 months was required. Presentation with MBC was defined as a DFI of zero. No prior chemotherapy for metastatic disease was allowed. A cumulative dose of up to 540 mg/m^2 doxorubicin prior to HDC was allowed. Required laboratory study results included leukocytes, 3000/mL; platelets, 100,000/mL; creatinine, 1.8 mg/dL; serum glutamic-oxaloacetic transaminase, 2.5 × normal; bilirubin, 1.5 × normal, and a cardiac ejection fraction, 50%. These studies were conducted according to the guidelines of the Dana Farber Cancer Institute and Beth Israel Hospital institutional review boards. Written informed consent was obtained. The schemas are provided in Table 1.

Trial I (Long Induction/Single Transplantation). In trial I [7], women were treated with standard chemotherapies, typically CAF (cyclophosphamide, doxorubicin, and fluorouracil) or AFM (doxorubicin, fluorouracil, and methotrexate), to best response. If they had achieved at least a partial response, they underwent stem cell collection (either marrow or chemotherapy/granulocyte-macrophage colony stimulating factor [GM-CSF]-mobilized peripheral blood progenitor cells [PBPC]), followed by high-dose CTCb (cyclophosphamide 1500 mg/m^2 per day × 4 days [total dose 6000 mg/m^2], thiotepa 125 mg/m^2 per day × 4 days [total dose 500 mg/m^2], and carboplatin 200 mg/m^2 per day × 4 days [total dose 800 mg/m^2] delivered by 96-hour continuous infusion).

Trial II (Long Induction/Double Transplantation). In trial II [25,26], women in partial or complete response to standard chemotherapies underwent marrow harvesting and stem cell mobilization with 2 cycles of AF (doxorubicin and 5-fluorouracil) with G-CSF. These patients then received 1 cycle of high-dose melphalan (140-180 mg/m^2) followed 3 to 5 weeks later by CTCb with marrow and PBPC support.

Trial III (Short Induction/Double Transplantation). In trial III [23,24], women with newly diagnosed MBC who were previously untreated with chemotherapy for metastatic disease were eligible. Induction/mobilization consisted of 2 cycles of doxorubicin, 30 mg/m^2 per day on days 1 to 3 given 14 days apart, with G-CSF, 5 μg/kg subcutaneously on days 4 to 12. In contrast to patients in trials I and II, patients in trial III with stable disease or better in response to induction were eligible to proceed with 2 cycles of HDC. HDC regimen I was CTCb. HDC regimen II (TxM) included taxol with dose escalation from 0 to 475 mg/m^2 given by 24-hour infusion on day 1 and melphalan 180 mg/m^2 in 2 divided doses given on day 3. The HDC regimens were given 5 weeks apart. TxM was given first in 32 patients, and CTCb was given first in 26 patients.

Post-Intensification Therapy

Surgery or radiation therapy to accessible sites of prior bulk disease (generally 3 sites or fewer) and/or first-, second-, or third-line hormonal therapy in patients with estrogen- or progesterone-receptor–positive disease were recommended after intensification. In trial III, bisphosphonate therapy was given to patients with bony metastases. Herceptin was not available for any of these trials.

Statistical Methods

All patients entered in trials were included in the outcome analysis. Standard response criteria were used, but with addition of the nCR category. CR required total disappearance of tumor and/or absence of tumor by surgical biopsy in persistent abnormalities for at least 4 weeks. nCR included VGPR (>90% reduction with persistent radiographic abnormalities felt to represent scar tissue), PR* (resolution of all soft tissue disease, but with residual abnormal bone scans with sclerotic lesions documented by radiograph or computed tomography), and NMD (all metastatic sites of disease were surgically resected or irradiated prior to induction chemotherapy) for at least 4 weeks. Partial response (PR) required 50% to 90% reduction of the product of perpendicular diameters of all measurable lesions for at least 4 weeks. Stable disease (SD) was defined as <50% reduction or <25% increase of the same parameters for ≥8 weeks, and disease progression (DP) required a ≥25% increase or the appearance of any new lesions. Response designations to induction chemotherapy did not include duration requirements. Time to failure was calculated from day on-study to the documentation of progression or death from any cause. Survival was calculated from day on-study to the documentation of death from any cause. Time to failure and survival were estimated

Table 2. *Patient Characteristics by Trial**

	Trial I Single Transplantation/ Long Induction	Trial II Double Transplantation/ Long Induction	Trial III Double Transplantation/ Short Induction	*P* Trial I/II Versus III
Years of trial	1988-1991	1991-1994	1994-1998	
No. of patients	62†	68†	58‡	
No. of transplantation patients	62	68	54	
Age, median (range), y	42 (27-57)	44 (28-55)	43 (31-55)	.31
ER–/PR–, no. (%)	32 (53%)	24 (38%)	19 (33%)	.10
ER+ or PR+/prior hormone therapy, no. (%)	22 (37%)	26 (41%)	20 (34%)	.53
ER+ or PR+/no prior hormone therapy, no. (%)	6 (10%)	13 (21%)	19 (33%)	.008
Unknown	2	5	0	
DFI, median (range), mo	18 (0-120)	26 (0-126)	24 (0-132)	.37
Prior (adjuvant) chemotherapy, no. (%)	40 (65%)	40 (59%)	37 (64%)	.77
Prior hormone therapy, no. (%)	29 (47%)	29 (43%)	24 (41%)	.65
No. of organs involved, median (range)	2 (1-5)	3 (1-6)	2 (1-10)	.20
Dominant sites of disease				
Visceral, no. (%)	33 (53%)	32 (47%)	25 (43%)	.38
Bone, no. (%)	8 (13%)	16 (24%)	16 (28%)	.15
Soft tissue, no. (%)	21 (34%)	20 (29%)	17 (29%)	.76

*ER indicates estrogen receptor; PR, progesterone receptor.

†Includes only patients completing high-dose therapy, eg, CR/PR only.

‡Includes all patients who entered trial whether or not they received high-dose therapy (intent-to-treat analysis).

using the Kaplan-Meier method [27]. Confidence intervals (CIs) were constructed around the Kaplan-Meier estimates using Greenwood's variance formula [28]. Univariate comparisons of these endpoints between patient groups based on pretransplantation characteristics, such as induction response, were made using the log-rank test [29]. Multiple factors were simultaneously assessed using proportional hazard regression [30]. However, because of small sample sizes, a lack of significance has a relatively low power to exclude a true association or vice versa.

RESULTS

Patient Characteristics

Between May 1988 and April 1998, we enrolled 188 women with MBC into 3 sequential trials of transplantation strategies: trial I (62 patients), trial II (68 patients), and trial III (58 patients). During this time frame, approximately 180 other women with MBC were enrolled into other transplantation trials. Reasons for not enrolling patients in trials I/II/III were related to stopping rules for phase I/II trials, patient unwillingness to go through a double transplantation, insurance decisions, or patients having already begun induction chemotherapy prior to being evaluated.

The characteristics of the patients entering each trial are summarized in Table 2, with the exception that more patients with estrogen receptor–positive tumors in trial III received no prior hormone therapy prior to chemotherapy ($P = .008$) than patients in trials I and II. The patient characteristics upon entry into these trials are similar, as were staging practices. Important differences in the trials were that only those patients achieving a partial response or better to induction therapy were enrolled and analyzed for trials I and II, but all patients were analyzed on an intent-to-treat basis for trial III, including those who did not receive intensification. Median patient age was 43 years (range, 27-57 years). One hundred seventeen patients (62%) had received prior adjuvant chemotherapy, 95 (48%) had presented with estrogen receptor– positive disease, of whom 65% had received prior hormonal therapy. The median DFI from initial presentation to onset of metastatic disease was 23 months (range, 0-132 months). The median number of organs involved was 2 (range, 1-10). Sites of disease included visceral dominant in 86 patients (46%), bone dominant in 40 patients (21%), and soft tissue only in the remainder of patients (30%).

Treatment

Patients in trials I, II, and III received a median of 4, 6, and 2 cycles of induction chemotherapy, respectively (Table 3). Only the patients with partial or better response were included in the analysis of trials I and II. All patients, whether they received transplants or not, were included in the analysis of trial III. In trial III, patients had not necessarily achieved maximal responses after only 2 cycles of induction therapy. Four patients (2%) died from toxicity (3 in trial I, 1 in trial II, and none in trial III).

Response to Therapy

In trials I, II, and III, CR/nCR rates to induction therapy were 42%, 56%, and 34%, respectively. Responses were measured after 4 to 6 induction cycles in trials I and II and after 5 weeks in trial 3. Best overall responses following completion of HDC included CR/nCR rates of 53%, 63%, and 76% for trials I, II, and III, respectively.

Event-Free Survival

Event-free survival (EFS) data are summarized in Table 3 and Figure 1. The median follow-up times for trials I, II, and III from day 1 of induction therapy were 98 months (range, 75-140 months), 62 months (range, 33-95 months), and

Table 3. *Response to Therapy and EFS and OS following Therapy*

Characteristic	Trial I Single Transplantation/ Long Induction	Trial II Double Transplantation/ Long Induction	Trial III Double Transplantation/ Short Induction
No. of patients	62*	68*	58†
No. of induction cycles, median (range)	4 (3-14)	6 (4-9)	2
Response to induction, no.			
CR	11 (18%)	17 (25%)	2 (3%)
nCR (VGPR/PR*/NMD)	15 (24%)	21 (31%)	18 (31%)
PR	36 (58%)	30 (44%)	23 (40%)
<PR	—	—	15 (26%)
Best overall response, no.			
CR	16 (26%) ┐ 53%	23 (34%) ┐ 63%	15 (26%) ┐ 76%
nCR (VGPR/PR*/NMD)	17 (27%) ┘	20 (29%) ┘	29 (50%) ┘
EFS and OS following therapy			
Median EFS, mo‡	8 {13}	11 {19}	24 {27}
3-year EFS, % (95% CI)	21 (6-36)	20 (5-35)	46 (37-55)
5-year EFS, % (95% CI)	15 (0-33)	14 (0-35)	46 (32-60)
Median OS, mo‡	25 {30}	23 {29}	54 {57}
3-year OS, % (95% CI)	42 (32-52)	43 (29-57)	66 (61-71)
5-year OS, % (95% CI)	29 (17-41)	28 (19-37)	50 (40-60)
Median follow-up, mo‡	92 {98}	55 {62}	36 {39}
Toxic death, no. (%)	3 (4.8%)	1 (1.5%)	0

*CR/PR only.

†All patients (intent to treat analysis).

‡From last HDC {from induction}.

39 months (range, 25-72 months), respectively, and from day 1 of last high-dose intensification were 92, 55, and 36 months, respectively. The median EFS times from induction chemotherapy were 13, 19, and 27 months for trials I, II, and III, respectively (III versus I + II, $P = .0004$; III versus I, $P = .0005$; III versus II, $P = .005$; II versus I, $P = .25$). The actuarial 3-year EFS rates from induction chemotherapy were 21% (95% CI, 6%-36%), 20% (95% CI, 5%-35%), and 46% (95% CI, 37%-55%) for trials I, II, and III, respectively. The actuarial 5-year EFS rates from induction chemotherapy were 15% (95% CI, 0%-33%), 14% (95% CI, 0%-35%), and 46% (95% CI, 32%-60%) for trials I, II, and III, respectively.

The characteristics of those patients remaining event free at the time of this report are summarized in Table 4.

Survival

Survival data are summarized in Figure 2. The median overall survival (OS) times from induction chemotherapy were 30, 29, and 39+ months for trials I, II, and III, respectively (III versus I and II, $P = .002$; III versus I, $P = .003$; III versus II, $P = .009$; II versus I, $P = .47$). Of the 65 patients alive, 44 remain event free at the time of this report. The actuarial 3-year OS rates from induction chemotherapy were 42% (95% CI, 32%-52%), 43% (95% CI, 29%-57%), and 66% (95% CI, 61%-71%) for trials I, II, and III, respectively. The actuarial 5-year OS rates from induction chemotherapy were 29% (95% CI, 17%-41%), 28% (95% CI, 19%-37%), and 50% (95% CI, 40%-60%) for trials I, II, and III, respectively.

Univariate and Multivariate Analysis for EFS and OS

Univariate and multivariate analysis for EFS and OS are summarized in Table 5. Age (<45, =45), DFI (0, 6-17 months, 8 months), estrogen receptor status (positive, negative, unknown), hormone responsiveness (negative receptors, positive receptors/prior hormone therapy, positive receptors/no prior hormone therapy), tumor grade (3 versus <3), prior chemotherapy (yes, no), sites of disease (visceral versus bony or soft tissue), number of organs involved (0-1 versus 2), response to induction therapy (CR versus nCR versus PR versus <PR), and trial (I versus II versus III) were analyzed for their association with EFS and OS.

By univariate analysis, participation in trial III, no prior adjuvant therapy, best response to long induction therapy (trials I and II only), no visceral disease, and fewer than 2 organs involved were favorable prognostic factors for EFS. Hormone sensitivity had borderline significance ($P = .06$). The same

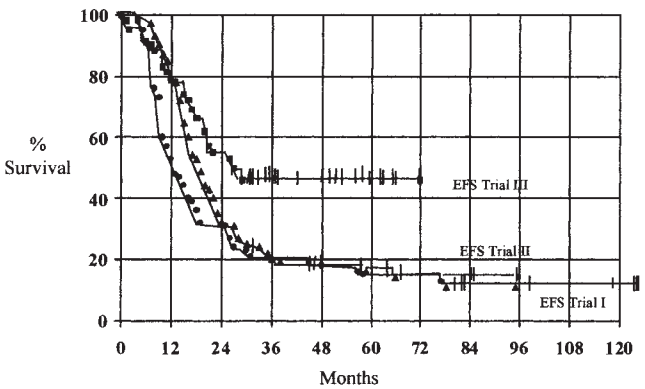

Figure 1. Event-free survival of metastatic breast cancer patients.

Table 4. *Characteristics of Event-Free and/or Living Patients**

Characteristics	On-Study	Event-Free	Alive
No. of transplantation patients	188†	44	65
Study I	62	8	11
Study II	68	9	18
Study III	58†	27	36
Age, median (range), y	43 (25-57)	43 (25-55)	44 (25-55)
Grade 3	96/121 (79%)	28/36 (78%)	39/52 (75%)
DFI, median (range), mo	24 (0-132)	23 (0-132)	23 (0-132)
DFI ≥24 months, no. (%)	93 (49%)	20 (45%)	29 (45%)
Prior (adjuvant) chemotherapy, no. (%)	117 (62%)	19 (43%)	33 (51%)
Hormone status (n = 181/42/63), no. (%)			
ER–/PR–	75 (40%)	18 (43%)	28 (44%)
ER+ or PR+/prior hormone	68 (36%)	13 (31%)	19 (30%)
ER+ or PR+/no prior hormone	38 (20%)	13 (31%)	18 (29%)
No. of organs involved, median (range)	2 (1-10)	2 (1-5)	2 (1-5)
Dominant sites of disease, no. (%)			
Visceral	90 (48%)	14 (32%)	22 (34%)
Bone	40 (21%)	15 (34%)	23 (35%)
Soft tissue	58 (31%)	15 (34%)	20 (31%)

*All patients analyzed on study, those event-free, and those still alive at time of analysis. Prior hormone indicates previously treated with at least 1 hormone therapy; DFI, disease-free interval from diagnosis to metastasis.

†Four patients did not undergo transplantation.

factors were associated with increased survival rates. Hormone sensitivity reached significance for survival ($P = .04$).

By multivariate Cox regression, participation in trial III and no prior adjuvant therapy remained favorable prognostic factors for both EFS and OS. Lack of visceral disease was also significant for better EFS only. Number of sites of disease and hormone sensitivity no longer contributed independently.

DISCUSSION

We have compared the EFS and OS of women with MBC treated with 3 sequential strategies of high-dose therapy: single transplantation/long induction, double transplantation/ long induction, and double transplantation/short induction. A small cohort (15% to 20%) of women remain progression free years after completion of the single transplantation therapy (trial I). The addition of single-agent high-dose melphalan into that framework extended the EFS and OS slightly during the first 2 years of follow-up, but did not affect long-term outcomes (trial II). Because trials I and II accepted only women in partial or better response, the total long-term survival rate of MBC might be estimated to be approximately 10% to 15% (approximately 70% of 15% to 20%). In contrast, the 5-year EFS rate is estimated as 46% (95% CI, 32%-60%) in trial III in an intent-to-treat analysis. The investigators are convinced that the population of women who entered these trials were highly selected motivated people but were not significantly different in personal or disease characteristics from one trial to the next. The multivariate analysis confirms that there were no significant differences in these populations to explain the substantial differences observed in outcomes. As shown in Table 3, lead-time bias could contribute to longer OS in the small excess of patients ($P = .008$) in trial III with estrogen receptor–positive tumors who had not had prior hormone therapy. Because these trials were not randomized comparisons but were sequential studies, we recognize that comparative analyses serve to generate hypotheses and to justify the conduct of definitive randomized trials that can define therapeutic advances.

Two features differentiate trial III from trials I and II: the addition of taxol and the use of short versus long induction. Taxol is a highly active agent against breast cancer, and it appears to provide at most a 2% absolute EFS advantage in locally advanced BC [31]. A single dose of taxol could contribute to the major differences observed between trial III and trials I and II. However, according to results with limited statistical power, there was also no obvious relationship between the taxol dose used and disease outcome, although there was an observed dose-toxicity relationship. More likely, the short induction and early intensification is the important clinical variable here [10,11,13,32].

In support of the concept of early intensification and

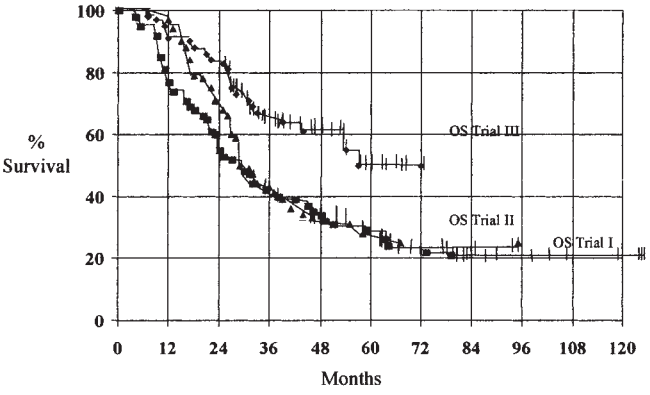

Figure 2. Overall survival of metastatic breast cancer patients.

Table 5. *Univariate and Multivariate Analysis of Prognostic Factors**

	EFS		OS	
	Hazard Ratio	*P*	Hazard Ratio	*P*
Univariate Analysis				
Regimen				
Double transplantation/short induction versus other (trial III versus I/II)	**2.09**	**.0004**	**2.06**	**.002**
Double/short versus double/long (trial III versus II)	**1.91**	**.005**	**1.97**	**.009**
Double/long versus single (trial II versus I)	**1.25**	**.25**	**1.16**	**.47**
Adjuvant chemotherapy (none versus some)	**1.87**	**.0005**	**1.66**	**.009**
No. cycles adjuvant chemotherapy ≤ 4 versus >4)	**1.6**	**.006**	**1.36**	**.09**
Soft tissue/bone versus visceral sites	**1.67**	**.003**	**1.63**	**.007**
No. organs (0-1 versus ≥ 2)	**1.45**	**.05**	**1.84**	**.004**
Response to long induction (CR/nCR versus other)	**1.77**	**.003**	**1.46**	**.07**
Response to short induction (CR/nCR versus other)	**1.65**	**.26**	**3.83**	**.03**
Hormone sensitivity (not treated & + versus ER– or treated)	**1.52**	**.06**	**1.64**	**.04**
Multivariate Analysis				
Regimen				
Double/Short Induction versus other (trial III versus I/II)		**.0008**		**.02**
Adjuvant chemotherapy (none versus some)		**.0001**		**.02**
Soft tissue/bone versus visceral sites		**.004**		**.39**
No. of organs (0-1 versus ≥ 2)		**.35**		**.10**
Hormone sensitivity (not treated & + versus ER– or treated)		**.49**		**.24**
DFI (0 versus other)		**.37**		**.74**

*Favorable factors are listed first.

the potential clinical impact of acquired acute drug resistance, Peters et al. conducted a randomized trial testing immediate versus delayed transplantation following induction therapy [32]. Patients with MBC received 4 cycles of AFM chemotherapy. Partial responders received immediate high-dose therapy. Nonresponders were removed from the protocol. Of the 25% who achieved a CR, a random half received high-dose therapy (using CBP, STAMP I [cyclophosphamide, cisplatin, and carmustine]) and the other half received high-dose therapy only after relapse. Immediate transplantation doubled the median duration of CR (8 versus 4 months). Of the relapsed patients, 50% achieved a second CR in response to transplantation. This second response was sufficient to provide a survival advantage trend over the immediate transplantation. These results lend support to the hypothesis that induction therapy induced drug resistance that reversed over time, such that the delayed transplantation became more effective a median of 4 months later.

Whether single-cycle high-dose therapy is more effective than conventional-dose therapy for the treatment of MBC responding to long induction remains controversial and awaits the completion and maturation of randomized trials. Two randomized trials reported have evaluated the role of high-dose therapy in MBC as either primary therapy or as consolidation after induction therapy [33,34]. One trial demonstrated an improvement in both disease free and overall survival with the use of high-dose therapy, but the results of this trial did not reach statistical significance because of the small sample size [33]. The other trial compared single-cycle transplantation using the CTCb regimen to 18 cycles of conventional-dose CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy in patients with at least a partial response to long induction chemotherapy and found no differences between the 2 treatments in EFS or OS [34]. Unfortunately, with only 184 evaluable and randomized patients, this trial had limited power to detect clinically significant and meaningful benefits. The lower than expected CR rate of 5% following CTCb and the low randomization rate of 55% may have contributed to poor overall outcomes. Additional larger and better powered randomized trials of single transplantation in responding patients are underway in Canada and Europe and will mature for analysis in several years.

In our experience, double transplantation/short induction is safe and feasible. All eligible patients completed both cycles of transplantation without treatment-related mortality or need for intensive care. Approximately 20% of patients managed their melphalan and taxol cycle entirely as outpatients. Treatment could be delivered within 14 to 16 weeks. The morbidity was sufficiently low to allow this regimen to be a framework upon which to build. Future directions include phase I efforts to add additional new agents to the transplantation regimens themselves (such as gemcitabine, temozolamide, and oxic agents) and immune therapeutic approaches in the peri-transplantation period [35].

Given the very favorable outcomes observed for patients with MBC absent treatment-related mortality, we believe the double transplantation/short induction regimen is ready for randomized comparison to standard therapies. Thus we have proposed a randomized comparison of this short induction/double transplantation regimen to standard therapy in patients with locally advanced BC in the cooperative group setting.

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