High-Dose Chemotherapy With Autologous Hematopoietic Stem-Cell Transplantation in Metastatic Breast Cancer: Overview of Six Randomized Trials

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See accompanying editorial on page 3205 and article on page 3214

ABSTRACT

Purpose

High doses of effective chemotherapy are compelling if they can be delivered safely. Substantial interest in supporting high-dose chemotherapy with bone marrow or autologous hematopoietic stem-cell transplantation in the 1980s and 1990s led to the initiation of randomized trials to evaluate its effect in the treatment of metastatic breast cancer.

Methods

We identified six randomized trials in metastatic breast cancer that evaluated high doses of chemotherapy with transplant support versus a control regimen without stem-cell support. We assembled a single database containing individual patient information from these trials. The primary analysis of overall survival was a log-rank test comparing high dose versus control. We also used Cox proportional hazards regression, adjusting for known covariates. We addressed potential treatment differences within subsets of patients.

Results

The effect of high-dose chemotherapy on overall survival was not statistically different (median, 2.16 v 2.02 years; $P = .08$). A statistically significant advantage in progression-free survival (median, 0.91 v 0.69 years) did not translate into survival benefit. Subset analyses found little evidence that there are groups of patients who might benefit from high-dose chemotherapy with hematopoietic support.

Conclusion

Overall survival of patients with metastatic breast cancer in the six randomized trials was not significantly improved by high-dose chemotherapy; any benefit from high doses was small. No identifiable subset of patients seems to benefit from high-dose chemotherapy.

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INTRODUCTION

Breast cancer is the most common malignant disease among women. It is the most prevalent cancer in the world, and globally, it is the leading cause of cancer mortality among women.¹ Although progress has been made in prolonging survival of patients with metastatic breast cancer (MBC), this stage of disease continues to be incurable. In the United States, the 5-year relative survival rate for women with MBC is 23%.²

In the 1980s and 1990s, oncologists attempted aggressive treatment strategies with the intent of improving long-term survival for women with breast cancer. Empirical evidence from in vitro and clinical

studies and mathematical modeling of clinical findings reported a positive correlation between tumor response rates and increased doses of alkylating agents.^{3,4} This provided scientific justification for clinical trials to evaluate high-dose chemotherapy (HDC) in the treatment of MBC. Autologous hematopoietic stem-cell transplantation (AHST) mitigated the treatment-induced problem of prolonged bone marrow suppression and the possibility of transplant-induced adverse graft reactions.

Several nonrandomized studies in the 1980s and 1990s suggested prolonged survival for women who received HDC with AHST.⁵⁻⁷ Those trials were subject to the many biases of patient selection, including differences in tumor staging. Nevertheless,

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Fig 1. Study selection process. BBCRG, Berlin Breast Cancer Research Group; ECOG, Eastern Cooperative Oncology Group; HDC, high-dose chemotherapy; IBDIS, International Randomized Breast Cancer Dose Intensity Study; NCIC, National Cancer Institute of Canada; PEGASE, Programme d'évaluation des greffes autologues dans le cancer du sein.

the use of AHST in the treatment of breast cancer in North America increased six-fold from 1989 to 1995, and breast cancer was the most common indication for AHST after 1992.⁸ Randomized controlled trials for MBC were initiated in the early 1990s to address the role of HDC with AHST versus a therapeutic regimen without stem-cell support (Ctrl). Accrual was slow and in some cases even failed.⁹ Reasons for the difficulties in accrual included the fact that HDC and Ctrl are different in terms of tolerability and perception of the potential

for cure. In 2001, a case of fraudulent reporting surfaced,¹⁰ which cast a pall over the concept. Early findings from randomized trials reported in 2000 and 2001 concluded no improved survival benefit attributable to HDC with AHST.^{11,12} In contrast, findings reported in 2003⁹ showed a high tumor response rate for patients with MBC assigned to HDC with AHST. Such contradictory findings contributed to the persistence of controversy regarding this treatment strategy.

During the years since HDC with AHST was first evaluated within and outside of randomized clinical breast cancer trials, this treatment strategy has received both unwavering support and unwavering opposition. Supporters have suggested that subpopulations of patients benefit from this therapeutic approach. However, randomized trials comparing HDC with Ctrl were initially too small to enable assessing such benefits. The ensuing years have allowed for the maturation of the randomized trials, providing more follow-up data to better inform evidence-based opinions regarding HDC with AHST in the treatment of MBC. To conduct a comprehensive analysis of these data, we assembled a database of patient-level information from the known randomized trials in MBC that addressed HDC with AHST versus a regimen consisting of conventional doses. We had two goals. One was to use the entirety of randomized information to maximize statistical power in addressing the possible role of HDC in the treatment of MBC. The second goal was to address whether there are identifiable subsets of patients who benefit from HDC.

METHODS

Trial selection criteria restricted the data to randomized trials that compared HDC with AHST with Ctrl in the treatment of MBC. We conducted a comprehensive review of the published literature using MEDLINE. In addition, we

Table 1. Trial Characteristics

Trial	Year of First Accrual	Year of Publication	Reference	Total No. of Patients	Length of Follow-Up (years)	Median Age (years)	Regimen (mg/m ² , unless otherwise indicated)			MDI		
							Induction	HDC	Ctrl	HDC	Ctrl	δ
ECOG	1990	2000	Stadtmauer et al ¹¹	199	2.2	47	If < 400 D prior, then 1,400 C, 60 D, 1,000 F; if 400-500 D prior, then 1,400 C, 80 Mt, 1,200 F	6,000 C, 500 T, 800 Cb over 4 days	If < 400 D prior, then 1,400 C, 60 D, 1,000 F; if 400-500 D prior, then 1,400 C, 80 Mt, 1,200 F	3.57	2.07	1.50
		2002	Stadtmauer et al ²⁰									
PEGASE 03	1995	2003	Roché et al ¹⁵	179	1.4	47	500 F, 500 C, 100 E	6,000 C, 800 T over 4 days	No further chemotherapy	2.85	0.00	2.85
		2008	Biron et al ²¹									
PEGASE 04	1995	2003	Roché et al ¹⁵	61	2.2	44	AN-based conventional chemotherapy	120 mg/kg C, 45 M, 140 A	AN-based conventional chemotherapy	5.28	2.34	2.94
		2005	Lotz et al ¹⁶									
NCIC	1997	2001	Crump et al ¹²	224	1.8	47	AN or TX	6,000 C, 70 M, 1,800 Cb over 4 days	AN or TX	6.60	2.09	4.51
		2008	Crump et al ²²									
IBDIS	1997	2003	Crown et al ⁹	110	2.4	46	50 D, 75 Doc	12,000 I, 18 AUC Cb, 1,200 Et, then 6,000 C, 800 T	1,200 C, 80 Mt, 1,200 F, four cycles	3.58	2.80	0.78
		2004	Crown et al ²³									
BBCRG	1998	2005	Schmid et al ¹⁷	93	2	50	—	45 M, 2,400 C (first course); 4,400 C (second course); 2,500 Et	60 D, 200 Pac $\leq$ six cycles, then optional 200 Pac, three cycles	3.96	2.93	1.03
Total				866	1.9	47						

Abbreviations: A, melphalan; AN, anthracycline; AUC, area under the curve; BBCRG, Berlin Breast Cancer Research Group; C, cyclophosphamide; Cb, carboplatin; Ctrl, control; D, doxorubicin; Doc, docetaxel; E, epirubicin; ECOG, Eastern Cooperative Oncology Group; Et, etoposide; F, fluorouracil; HDC, high-dose chemotherapy; I, iphosphamide; IBDIS, International Randomized Breast Cancer Dose Intensity Study; M, mitoxantrone; MDI, maximum dose-intensity; Mt, methotrexate; NCIC, National Cancer Institute of Canada; Pac, paclitaxel; PEGASE, Programme d'évaluation des greffes autologues dans le cancer du sein; T, thiotepa; TX, taxane.

reviewed presentations at all annual meetings of the American Society of Clinical Oncology. We consulted the European Blood and Marrow Transplant Group and the American Society for Blood and Marrow Transplantation to confirm the thoroughness of our review. We also compared our results with those in reviews published by The Cochrane Collaboration.^{13,14} Our search process (Fig 1; Appendix, online only) identified six trials.^{9,11,12,15-17} The trials were initiated between 1990 and 1998. We solicited and received individual patient data from all six trialists. We merged these data into a single database, taking care to record information about the original trial for each patient, along with patient-specific covariates. Data included demographic and clinical characteristics, trial characteristics, treatment characteristics, and outcome variables. Our study was approved by the MD Anderson Cancer Center institutional review board.

The protocol-specified primary end point was overall survival (OS), and the secondary end point was progression-free survival (PFS). OS is the time from randomization to death as a result of any cause or date of last follow-up. PFS is the time from randomization to disease progression or death as a result of any cause or date of last follow-up. Survival postprogression (SPP) is the difference in those measures (ie, OS – PFS). We determined Kaplan-Meier estimates of OS, PFS, and SPP by treatment group. For OS, we also determined Kaplan-Meier estimates within the individual trials by patient subset. The primary analysis of the treatment comparison is the log-rank test. Our study has 86% statistical power to detect a 20% relative reduction in risk of death (hazard ratio [HR], 0.80) for HDC as opposed to Ctrl.

Recognizing that there are differences among the trials and among patients within the trials, as a secondary analysis, we adjusted for these differences using a multivariate Cox proportional hazards regression model. We considered the treatment group (HDC v Ctrl) and the following prespecified covariates: (1) the trial (as a random effect), (2) age at random assignment, (3) disease-free interval (time from initial diagnosis of breast cancer to diagnosis of MBC), (4) time from metastasis to randomization, (5) performance status at randomization, (6) number of sites of metastasis, (7) hormone receptor status of the primary tumor, and (8) prior chemotherapy. Missing data for the covariates were multiply imputed,¹⁸ but multiple imputation was not used for subset analyses. *P* values were generated with the MIANALYZE procedure in SAS 9.1 (SAS Institute, Cary, NC). The comparison of principal interest in this multivariate model is the HR of HDC to Ctrl. We determined 95% CIs for the covariate-adjusted HRs.

We provide unadjusted Kaplan-Meier estimates of OS and PFS for HDC and Ctrl for subgroups defined by prognostic factors that had significant interactions with the treatment group. In addition, we provide Kaplan-Meier estimates of OS for HDC versus Ctrl for the following factors of clinical interest, whether or not they evinced statistical significance: hormone receptor status, number of sites of metastasis (one site v > one), and sites of metastases (bone only and lung only). For presentation purposes, we categorized the metastatic sites as follows: bone only, soft tissue (chest wall, contralateral lymph nodes), visceral (CNS, liver, and lung), and other. Recognizing the multiplicity of comparisons, we provide neither *P* values nor CIs for survival probability by subgroup of patients.

Doses and scheduling of chemotherapy drugs varied across the six trials; hence, the labels of HDC and Ctrl represent ranges in therapeutic approaches. Some trialists used induction therapy, and some did not. Some control regimens were open ended, with patients treated until progression or death, whereas others involved no chemotherapy after induction. Some trialists used two cycles of HDC in tandem. To partially account for differences in the regimens, we calculated the maximum dose-intensity (MDI)¹⁹ in milligrams per meter squared per week in one cycle of the treatment phase of each group within each trial as a single number representing dose-intensity. We used the MDI in place of the HDC and Ctrl in multivariate modeling to indicate the results per unit increment in the MDI.

All randomly assigned patients were included in the analysis based on the principle of intention to treat. *P* values are based on two-sided tests, with *P* ≤ .05 considered significant. SAS 9.1 (SAS Institute) and S-Plus version 7.0 (Insightful Corporation, Seattle, WA) were used in statistical analyses.

Table 2. Patient Demographics and Clinical Characteristics

Characteristic	HDC (n = 447)		Ctrl (n = 419)	
	No.	%	No.	%
Age, years				
Median	46.2		46.0	
Range	21.7-66.1		20.6-67.0	
< 50	295	66.0	263	62.8
≥ 50	130	29.1	155	37.0
Missing	22	4.9	1	0.2
Prior hormonal therapy				
No	263	58.8	252	60.1
Yes	137	30.6	143	34.1
Missing	47	10.5	24	5.7
Prior chemotherapy				
No	200	44.7	195	46.5
Yes	239	53.5	218	52.0
Missing	8	1.8	6	1.4
Prior radiation therapy				
No	188	42.1	174	41.5
Yes	187	41.8	196	46.8
Missing	72	16.1	49	11.7
ECOG performance status				
0	216	48.3	205	48.9
1-2	101	22.6	92	22.0
Missing	130	29.1	122	29.1
Hormone receptor status				
Negative	103	23.0	129	30.8
Positive	225	50.3	188	44.9
Missing	119	26.6	102	24.3
Menopausal status				
Pre	96	21.5	111	26.5
Post	211	47.2	214	51.1
Missing	140	31.3	94	22.4
No. of metastatic sites				
1	182	40.7	158	37.7
≥ 2	265	59.3	261	62.3
Soft tissue metastasis				
No	188	42.1	169	40.3
Yes	226	50.6	220	52.5
Missing	33	7.4	30	7.2
Bone metastasis				
No	175	39.1	151	36.0
Yes	208	46.5	220	52.5
Missing	69	14.3	48	11.5
Visceral metastasis				
No	146	32.7	150	35.8
Yes	271	60.6	253	60.4
Response after induction				
CR + PR	260	58.2	260	62.1
SD + PD	45	10.1	47	11.2
Missing	142	31.8	112	26.7
Median disease-free interval, years*	2.5		2.4	
MBC as initial diagnosis†				
No	322	72.0	315	75.2
Yes	46	10.3	45	10.7
Missing	79	17.7	59	14.1

Abbreviations: CR, complete response; Ctrl, control; ECOG, Eastern Cooperative Oncology Group; HDC, high-dose chemotherapy; MBC, metastatic breast cancer; PR, partial response; PD, progressive disease; SD, stable disease.

*Time from initial diagnosis to metastasis.

†Disease-free interval < 1 month.

RESULTS

Table 1 lists the characteristics of the six randomized trials we considered. No two trials used the same HDC or Ctrl regimen. In one trial (PEGASE [Programme d'évaluation des greffes autologues dans le cancer du sein] 03^{15,21}), patients randomly assigned to Ctrl received induction chemotherapy but no further therapy. Two trials (IBDIS [International Randomized Breast Cancer Dose Intensity Study]^{9,23} and BBCRG [Berlin Breast Cancer Research Group]¹⁷) used tandem HDC courses, whereas the others used a single HDC course. The BBCRG trial differed from the others in that investigators randomly assigned patients to HDC or Ctrl without first administering induction chemotherapy. In the other five trials, all patients received induction chemotherapy and were then randomly assigned to HDC versus Ctrl only if they had responded to the induction regimen (by achieving either complete or partial response without disease progression).

A total of 866 women with MBC were included in our study: 447 randomly assigned to the HDC and 419 to Ctrl. Their characteristics are listed in Table 2 by treatment arm. Prognostic factors were well

balanced between the HDC and Ctrl groups, except for hormone receptor status (limited to patients with reported hormone receptor status: 69% positive in HDC v 59% in Ctrl).

Figure 2A presents Kaplan-Meier estimates of OS for the HDC and Ctrl groups within the six individual trials. Figure 2B is a forest plot of the HRs of OS (left panel) and PFS (right panel) by the difference in MDI between the HDC and Ctrl groups, plotted by trial. The thicknesses of the plotted lines are proportional to the numbers of patients in the trials.

Figure 3A shows OS for the six trials combined. Unadjusted for prognostic characteristics and trial differences, the treatment effect was not statistically significant (HR, 0.87; 95% CI, 0.75 to 1.02; $P = .08$). Figure 3B shows PFS for all six trials combined. PFS is significantly longer for HDC (median, 11.0 months) than for Ctrl (8.3 months), with an HR of 0.76 (95% CI, 0.66 to 0.88; $P < .001$). Figure 3C shows SPP for HDC and Ctrl. Median duration of SPP was approximately 1 year in both groups.

Table 3 gives the results of the multivariate Cox proportional hazards model for OS. Missing covariate information was multiply

Fig 2. Survival by trial. (A) Kaplan-Meier estimates of overall survival (OS) by trial. Hazard ratios (HRs) are presented with 95% CIs. P values are from the log-rank test. (B) Adjusted HRs of OS and progression-free survival (PFS) for high-dose chemotherapy (HDC) and control therapy (Ctrl) versus differences in maximum dose-intensity (MDI). BBCRG, Berlin Breast Cancer Research Group; ECOG, Eastern Cooperative Oncology Group; IBDIS, International Randomized Breast Cancer Dose Intensity Study; NCIC, National Cancer Institute of Canada; PEGASE, Programme d'évaluation des greffes autologues dans le cancer du sein.

Fig 2. continued.

imputed. The two covariates with greatest proportions of missing data were performance status (29%) and hormone receptor status (26%). Results are presented as the HR for OS based on the indicated comparison with 95% CIs. The adjusted HR of OS comparing HDC with Ctrl was 0.89 (95% CI, 0.76 to 1.04; $P = .13$). After adjusting for trial, age, and hormone receptor status, the HR per unit increase of MDI was 0.94 (95% CI, 0.89 to 1.00; $P = .046$). As regards PFS, after adjusting for trial, age, and hormone receptor status, the HR of HDC compared with Ctrl per unit increase in MDI was 0.88 (95% CI, 0.84 to 0.93; $P < .001$).

Multivariate proportional hazards modeling suggested an interaction between treatment and the following covariates: age

(≥ 50 years $v < 50$), menopausal status (pre v post), and soft tissue metastases (yes v no). Figure 4 compares HDC versus Ctrl for these subgroups as well as hormone receptor status, number of sites of metastasis, bone-only metastases, and lung-only metastases. Consistent with the significant interactions in multivariate models, Figure 4 suggests a benefit for HDC in patients younger than 50 years of age, premenopausal patients (which is highly correlated with age), patients with soft tissue metastases, and patients with two or more sites of metastasis. However, these associations are weak, with modest absolute differences in OS. In particular, the interactions are not sufficiently robust to withstand adjustments for multiple comparisons.

Fig 3. Kaplan-Meier estimates of survival outcomes based on data from all six trials. (A) Overall survival (OS); (B) progression-free survival (PFS); (C) survival postprogression (SPP). Hazard ratios (HRs) are presented with 95% CIs. P values are from the log-rank test. Ctrl, control therapy; HDC, high-dose chemotherapy.

Table 3. Multivariate Cox Proportional Hazards Model of Overall Survival With Multiple Imputation of Missing Values

Factor	HR	95% CI	P
HDC v Ctrl	0.89	0.76 to 1.04	.13
Age (≥ 50 v < 50 years)	1.05	0.88 to 1.24	.61
No. of metastatic sites (≥ 2 v 1)	1.36	1.15 to 1.61	< .001
Disease-free interval, per year	0.96	0.93 to 0.99	.0078
Metastatic interval, per year*	1.00	0.92 to 1.08	.93
ECOG performance status (1-2 v 0)	1.26	1.06 to 1.50	.0096
Hormone receptor status (positive v negative)	0.67	0.56 to 0.81	< .001
Prior chemotherapy (yes v no)	1.64	1.39 to 1.94	< .001

Abbreviations: Ctrl, control; ECOG, Eastern Cooperative Oncology Group; HDC, high-dose chemotherapy; HR, hazard ratio.

*Diagnosis of metastasis to randomization.

DISCUSSION

Vogl et al,²⁴ among others, have posited that HDC is a therapy the time for which has passed. Other breast cancer researchers have continued to support its further evaluation in specific subgroups of patients.²⁵ In view of the relatively small sample sizes, no single trial randomly allocating patients with MBC to HDC versus Ctrl has had much statistical power. The conclusion of individual trials has left open the possibility of a rather large benefit for HDC. Literature-based meta-analyses are handicapped by having to combine gross summary statistics such as Kaplan-Meier survival plots across trials and by the inability to account appropriately for trial and patient heterogeneity. And they cannot identify subsets of patients who might benefit from

Fig 4. Kaplan-Meier estimates of the overall survival (OS) comparison of patients with metastatic breast cancer who received high-dose chemotherapy (HDC) versus control therapy (Ctrl) in subset analyses. (A) Age younger than 50 years; (B) age 50 years or older; (C) premenopausal; (D) postmenopausal; (E) soft tissue metastasis; (F) no soft tissue metastasis; (G) hormone positive; (H) hormone negative; (I) one metastatic site; (J) two or more metastatic sites; (K) bone-only metastasis; (L) lung-only metastasis.

HDC. We therefore carried out a meta-analysis based on individual patient data from relevant randomized trials.

Our study involving 866 women with MBC suggests a small nonsignificant OS difference between HDC and Ctrl ($P = .08$). The P value actually increased on accounting for patient covariates (HR, 0.89; $P = .13$). The trials compared treatment regimens with different relative dose intensities. Quantifying this difference using MDI produced a marginally significant dose effect for OS ($P = .046$).

Searching for subsets in which a particular therapy may be beneficial is problematic in the context of a study that is negative overall. Any such subset is likely to be small. We have not included significance levels for subgroup analyses out of consideration of multiplicity. The differences shown in the various comparisons of Figure 4 are typical of variability across subsets in clinical research and do not make the case that HDC is effective in any particular subset of patients.

We observed a statistically significant advantage for HDC in terms of PFS (HR, 0.76; $P < .001$). However, this advantage did not translate into a survival benefit. This was despite no difference between HDC and Ctrl in terms of survival after progression. Median duration of SPP was approximately 1 year in both groups. This observation is an illustration of the effect described by Broglio et al.²⁶ As in the simulated first example that article, adding SPP with a distribution that is the same in both groups to a significant difference in PFS results in a loss of statistical significance. In effect, the duration of SPP adds noise that dilutes the observed effect on PFS.²⁶

Our study has limitations. One is that not all breast cancer therapies currently available were evaluated in the trials. Also, the biomarker information available to us was limited. We had hormone receptor status for most of patients but insufficient information about human epidermal growth factor receptor 2 status and no information about other biomarkers.

A retrospective review compared 635 patients with MBC from four CALGB (Cancer and Leukemia Group B) trials with 441 similar patients from the Autologous Blood and Marrow Transplant Registry.²⁷ Although this earlier analysis was subject to the usual biases associated with cross-database comparisons, the earlier results were qualitatively similar to those in the present overview of randomized trials. Interestingly, the Ctrl group from the earlier study (ie, the four CALGB trials) and the Ctrl group from the six randomized trials of HDC had essentially identical OS distributions. On the other hand, OS at years 4 and 5 for HDC patients in the earlier study was somewhat greater than that in the present study. The observation in the present study (Fig 4) of a possible benefit with HDC in patients with soft tissue disease is not borne out by the earlier study, further suggesting that this observation is spurious.

For patients with MBC who participated in the six randomized trials, OS was not significantly improved by use of HDC with AHST. Any benefit of HDC as used in these trials was small or nonexistent. It remains an open question whether drugs not considered in these trials would provide benefit into dose ranges that require AHST, or whether combining new biologic therapies with HDC would enhance its effect.

Our conclusion in this article that HDC does not have a statistically significant benefit in OS is supported by the conclusion in our companion report²⁸ that HDC as adjuvant therapy does not have a statistically significant benefit in OS in primary breast cancer. Both of our studies leave open the possibility of a modest reduction in the hazards of OS in the range of 5% to 10%, but neither was able to identify subsets of patients who may benefit from HDC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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