original research report

Long-term survival after high-dose chemotherapy with autologous hematopoietic cell transplantation in metastatic breast cancer

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OBJECTIVE/BACKGROUND: The most common indication for high-dose chemotherapy (HDC) and autologous hematopoietic cell transplantation (AHCT) in the 1990s was breast cancer. Several randomized trials and a more recent meta-analysis failed to show a survival benefit for AHCT in metastatic breast cancer (MBC); however, they demonstrated a better-than-expected 10-year to 15-year survival in 5–15% of patients. We thus evaluated the long-term results of treatment with HDC and AHCT in MBC at our institution.

METHODS: From 1984 to 2000, 285 patients underwent AHCT for MBC. The patient characteristics were collected through the Cleveland Clinic, United Transplant Database. A retrospective review of the medical records of the long-term surviving breast-cancer patients treated with HDC and AHCT was conducted.

RESULTS: With a median follow-up of 169 months, 34 (12%) remain alive. Of the 251 patients who died, 218 (87%) died of metastatic disease. A comparison by age (<50 years and >50 years) and hormonal status did not demonstrate any differences in relapse ($p = .33$ and $p = .32$, respectively) or survival ($p = .13$ and $p = .42$). Of the 34 long-term survivors, sufficient data were available on 28 patients, and further evaluation revealed that the majority had a primary or locally recurrent oligometastatic disease.

CONCLUSION: This retrospective evaluation of patients who underwent AHCT for MBC demonstrates long-term survival in a small subset of patients, primarily those with primary or recurrent oligometastatic disease. Oligometastatic breast cancer is a distinct entity within MBC, which may be curable with multimodality therapy. We thus conclude there remains no overall-survival benefit to HDC in MBC.

KEYWORDS: Autologous hematopoietic cell transplant; High-dose chemotherapy; Oligometastatic breast cancer

Despite advances in the diagnosis and treatment for breast cancer over the last several decades, metastatic breast cancer (MBC) is the leading cause of cancer death in women in developed countries.[1,2] MBC is a heterogeneous disease that may range from solitary metastatic lesions to diffuse multiorgan involvement. Preclinical studies published in the early 1980s demonstrated a steep dose–response effect predicting for greater cytotoxicity with increasing dose intensity of antitumor agents, such as alkylating agents and antimetabolites.[3] These data served as the basis for the use of high-dose chemotherapy (HDC) with autologous hematopoietic cell transplantation (AHCT) for a variety of solid

tumors. Several nonrandomized studies in the mid-1980s and early 1990s suggested a prolonged survival for women with breast cancer who received HDC with AHCT.[4–6] These trials were subject to biases, including patient selection,[7] and subsequent randomized Phase III trials were performed to address the role of HDC in MBC. Owing to poor accrual, these trials were relatively small, and did not show a significant survival advantage for HDC compared to conventional chemotherapy.[8–12] Many of these trials were underpowered to detect realistic differences; however, a recently published meta-analysis from the six MBC randomized trials comparing HDC with conventional therapy without stem-cell support confirmed a lack of significant survival advantage and failed to identify any subset of patients who benefited from this approach. Regardless, many of these trials[8–12] demonstrate a better-than-expected 10-year to 15-year progression-free and overall survival (OS) occurring in a small subset (5–15%) of patients. There thus remains controversy as to whether specific subsets of MBC patients may benefit from HDC. These data prompted us to evaluate the long-term results and the survivors of treatment with HDC and AHCT in MBC at our institution.

MATERIALS AND METHODS

Patients

Four hundred ninety-one patients underwent HDC followed by AHCT for breast cancer from 1984 to 2000 at the Cleveland Clinic, Taussig Cancer Institute. Among these, 285 were diagnosed as having metastatic stage IV disease according to the American Joint Committee on Cancer staging guidelines prior to 2000. All patients met the minimal criteria for eligibility to proceed with HDC and AHCT per our standard and protocol guidelines. All study patients provided a signed informed consent, and were treated on protocols approved by the institutional review board.

Transplant regimens

STAMP-V (cyclophosphamide [Cy] given by intravenous infusion at 1500 mg/m^2 daily × 4 days; carboplatin, 200 mg/m^2 × 4 days; and thiotepa [TT], 125 mg/m^2 × 4 days), $n = 177$, was the predominant preparative regimen given prior to AHCT. Other conditioning regimens included busulfan (1 mg/kg orally every 6 h × 16 doses) and Cy (60 mg/kg intravenous infusion × 2 days), $n = 54$; STAMP-I (Cy, given intravenously at 1875 mg/m^2 × 3 days; cisplatin, 55 mg/m^2 × 3 days; and bis-chloronitrosourea (BCNU), 600 mg/m^2 given for one dose), $n = 26$; and either high-dose TT or BCNU alone ($n = 28$).

Study design

The patient clinical and transplant characteristics were collected through the Cleveland Clinic, Taussig Cancer Institute, United Transplant Database. A retrospective review of the medical records of the long-term surviving breast-cancer patients treated with HDC and AHCT was also conducted. The data collected included patient demographics, characteristics of the primary and recurrent tumor, axillary nodal status, prior adjuvant chemotherapy, hormone-receptor status, extent of metastatic disease, and patient outcome. The combined hormone-receptor status was considered negative if both estrogen receptors (ERs) and progesterone receptors (PRs) were negative, and positive if either one or both were positive. Information was not available regarding the human epidermal-growth-factor receptor 2 (HER2) status.

Statistical analysis

Three outcomes were assessed: relapse, OS, and relapse-free survival (RFS). Events corresponding to these three outcomes were relapse, all-cause mortality, and relapse or all-cause mortality, respectively. The outcomes were calculated from the date of transplant to the date of the event or the date of the last follow-up. Because age and ER/PR status are often prognostic factors in breast cancer, the outcomes were compared by age (<50 years and ≥50 years) and ER/PR status (positive vs. negative) using log-rank tests. A continuous variable was calculated for years since the first study transplant to account for potential changes in outcomes over the study duration. Cox proportional hazards analysis was used to identify significant prognostic factors. For the multivariable analysis, a stepwise-selection procedure was used with a variable entry criterion of $p \leq .10$ and a variable retention criterion of $p \leq .05$. The Cox results are summarized as the hazard ratio (HR) and 95% confidence interval (CI) for the HR. The data were analyzed using the SAS software (SAS Institute, Inc., Cary, NC, USA). All statistical tests were two sided, and $p \leq .05$ was used to indicate statistical significance.

RESULTS

The patient and transplant characteristics are shown in Table 1. The median age was 44 years (range: 24–65 years), and the overwhelming majority was female (99%). The majority of patients had a

Table 1. Patient and transplant characteristics.

Variable	*N* (%)
Gender	
Female	282 (99)
Male	3 (1)
Race ($n = 240$)	
White	230 (96)
Black	10 (4)
Age at transplant (years)	
Mean ± SD	44 ± 7
Median (range)	44 (24–65)
Karnofsky performance status ($n = 273$)	
80	7 (3)
90	255 (93)
100	11 (4)
Number of prior chemotherapy regimens	
1	86 (30)
2	155 (54)
3	34 (12)
4	7 (3)
5	3 (1)
Prior radiation therapy	
Yes	159 (56)
No	126 (44)
Months from diagnosis to transplant	
Mean ± SD	42 ± 34.5
Median (range)	33.2 (3–201)
Disease status at transplant	
CR	155 (54)
PR	122 (43)
Relapsed/refractory	8 (3)
ER/PR status ($n = 242$)	
Positive	161 (67)
Negative	81 (33)
Number of positive nodes ($n = 261$)	
Mean ± SD	16 ± 8
Median (range)	14 (1–42)
Cell source	
PBSC	235 (83)
BM	35 (12)
PBSC + BM	15 (5)
Preparative regimen	
STAMP-V	177 (62)
Bu/Cy	54 (19)
Cis/Cy/BCNU	26 (9)
Other	28 (10)
CD34 + dose $\times 10^6$/kg ($n = 186$)	
Mean ± SD	4.91 ± 4.22
Median (range)	3.24 (.37–29.71)
Patient status at follow-up	
Alive	34 (12)
Dead	251 (88)
Secondary malignancy	
Yes	4 (1)
No	281 (99)
Cause of death ($n = 251$)	
Relapse	218 (87)
Infection	4 (2)
Pulmonary toxicity	3 (1)
Cardiac	3 (1)
Secondary malignancy	2 (.8)
VOD	2 (.8)
CNS bleed	1 (.4)
Unknown	18 (7)

BCNU = bis-chloronitrosourea; BM = bone marrow; Bu/Cy = busulfan/cyclophosphamide; Cb = carboplatin; Cis = cisplatin; CNS = central nervous system; Cy = cyclophosphamide; PBSC = peripheral-blood stem cell; TT = thiotepa; VOD = veno-occlusive disease.

Table 2. Univariate model for relapse, relapse-free survival, and overall survival.

Variable	Relapse			Relapse-free survival			Overall survival		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Sex									
Male/female	0.75	.10–5.36	0.77	2.05	.65–6.42	0.22	2.36	.75–7.38	0.14
Race (N = 240)									
Black/white	0.5	.22–1.13	0.1	0.61	.30–1.24	0.17	0.64	.30–1.35	0.24
Age at transplant (years)									
≥50/<50	1.16	.86–1.57	0.33	1.2	.90–1.60	0.21	1.25	.94–1.67	0.13
Karnofsky performance status (N = 273)									
Per 10-point increase	0.87	.49–1.55	0.64	0.79	.45–1.39	0.41	0.64	.36–1.15	0.14
Number of prior chemotherapy regimens									
Per one increase	1.5	1.27–1.77	<.001	1.43	1.22–1.68	<.001	1.41	1.20–1.65	<.001
Prior radiation therapy									
Yes/no	1.09	.84–1.42	0.5	1.07	.84–1.37	0.6	1.14	.88–1.46	0.31
Months from diagnosis to HCT									
Per 12-month increase	1.02	.98–1.07	0.26	1.02	.98–1.06	0.36	1.03	.99–1.07	0.17
Disease status at transplant									
Partial remission/CR	1.54	1.18–2.00	0.001	1.56	1.21–2.00	<.001	1.57	1.21–2.02	<.001
Relapsed/refractory/CR	1.73	.76–3.94	0.19	2.15	1.05–4.40	0.036	2.56	1.24–5.26	0.011
ER/PR status (N = 242)									
Positive/negative	0.86	.64–1.16	0.32	0.95	.72–1.26	0.73	0.89	.66–1.18	0.42
Number of positive nodes (N = 261)									
Per one node increase	1	.98–1.02	0.7	1	.98–1.02	0.78	1	.98–1.02	0.89
Cell source									
BM/PBSC + BM	1.85	.90–3.81	0.09	2.38	1.22–4.63	0.011	2.45	1.23–4.87	0.011
PSC/PBSC + BM	1.31	.72–2.42	0.38	1.35	.75–2.43	0.31	1.38	.75–2.54	0.3
Preparative regimen									
STAMP-V/other	0.68	.42–1.11	0.12	0.53	.35–.80	0.003	0.53	.35–.80	0.003
Bu/Cy/other	0.69	.40–1.20	0.19	0.55	.34–.89	0.015	0.67	.42–1.08	0.1

Table 2. (Continued).

Variable	Relapse			Relapse-free survival			Overall survival		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Cis/Cy/BCNU/other	0.44	.24–.84	0.011	0.33	.19–.59	<.001	0.34	.19–.60	<.001
Years since first transplant									
Per 5-year increase	0.92	.73–1.16	0.47	0.81	.66–1.01	0.06	0.75	.61–.93	0.007

BCNU = bis-chloronitrosourea; BM = bone marrow; Bu = busulfan; CI = confidence interval; Cis = cisplatin; CR = complete remission; Cy = cyclophosphamide; ER = estrogen receptor; HCT = hematopoietic cell transplantation; HR = hazard ratio; PBSC = peripheral-blood stem cell; PR = progesterone receptor.

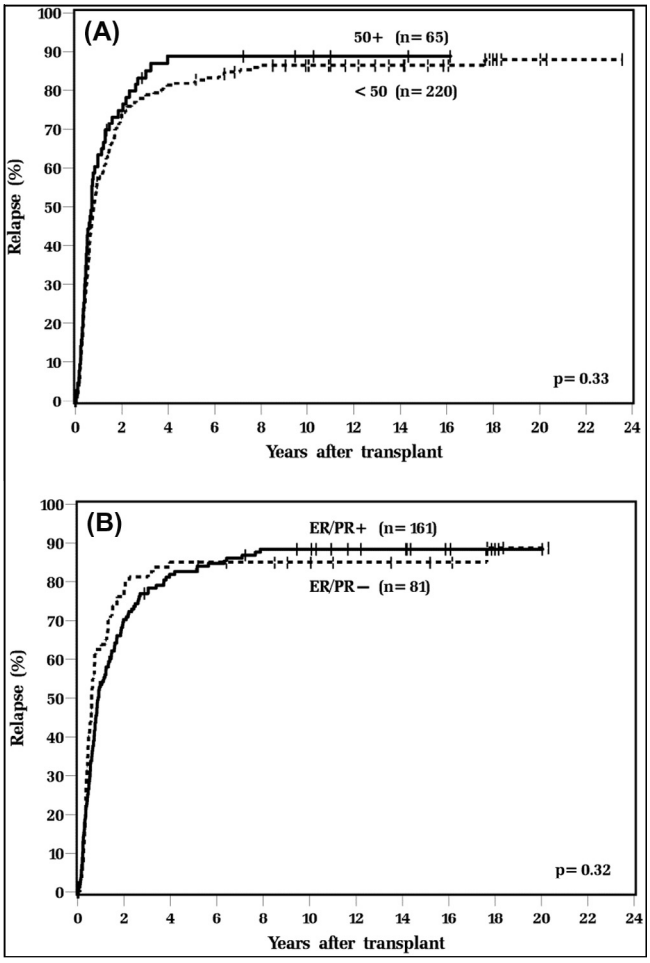

Figure 1. Cumulative incidence of relapse after high-dose chemotherapy and autologous hematopoietic cell transplantation in (A) metastatic-breast-cancer patients <50 years of age and ≥50 years of age, and (B) patients with estrogen-receptor/progesterone-receptor-positive and estrogen-receptor/progesterone-receptor-negative tumors. ER = estrogen receptor; PR = progesterone receptor.

Karnofsky performance status of at least 90%. About 70% of the patients received more than one prior chemotherapy regimen, which primarily consisted of the combination with Cy, Adriamycin, and 5-fluorouracil; Cy, methotrexate, and 5-fluorouracil; or Adriamycin and Cy; and 56% had received prior

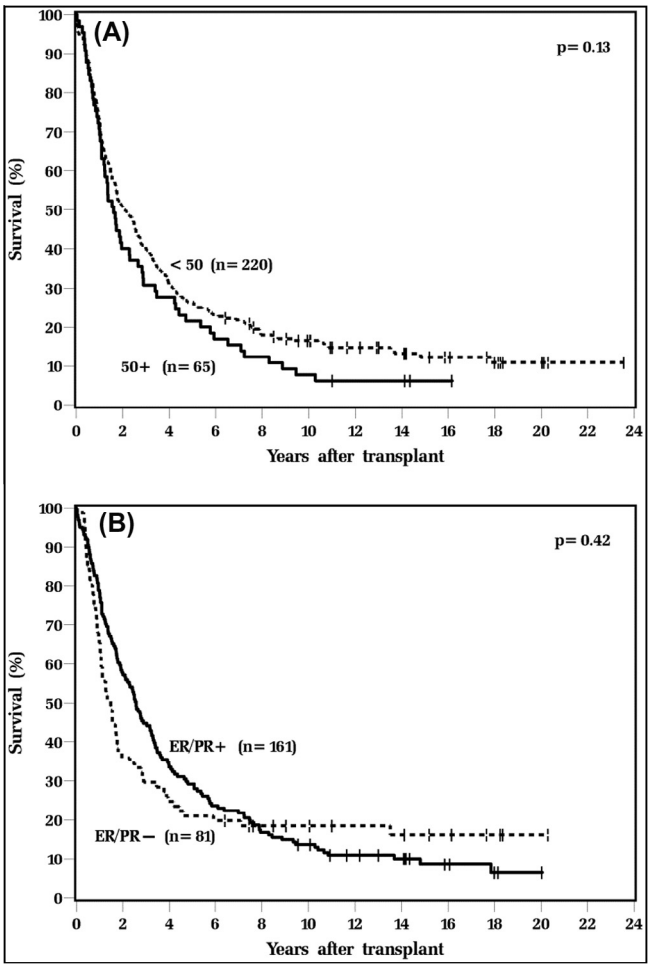

Figure 2. Kaplan–Meier curve of overall survival after high-dose chemotherapy and autologous hematopoietic cell transplantation in (A) metastatic-breast-cancer patients <50 years of age and ≥50 years of age, and (B) patients with estrogen-receptor/progesterone-receptor-positive and estrogen-receptor/progesterone-receptor-negative tumors. ER = estrogen receptor; PR = progesterone receptor.

radiation therapy. Fifty-four percent of the patients were in a complete remission (CR) prior to HDC, while 43% achieved a progesterone receptor and 3% were relapsed or refractory prior to HDC. The majority (83%) of the patients received peripheral-blood stem cells (PBSCs), 12% received bone marrow (BM), and 5% received a combination of both PBSCs and BM. Approximately 62% of the patients received STAMP, 19% busulfan/Cy, 9% cisplatin/Cy/BCNU, and 10% other, including single agent TT or BCNU. The median CD34 + dose given to the patients was 3.24×10^6/kg (range: 0.37–29.71). The median length of hospital stay was 21 days (range: 7–90 days). The median time after transplant to reach an absolute neutrophil count $>0.5 \times 10^9$/L and platelet count $>20 \times 10^9$/L was 11 days (range: 8–48 days) and 13 days (range: 8–139 days), respectively.

With a median follow-up of 169 months (range: 77–283 months) in survivors, 34 (12%) of these patients remain alive. Of the 251 patients who died, 218 (87%) died of relapsed/metastatic disease. Other causes of death included infectious or cardiopulmonary etiologies. The incidence of death from secondary malignancies was less than 1%. HER2 status was unavailable in the majority of the patients, but a comparison by age (<50 and ≥ 50) and hormonal status did not demonstrate any significant differences in relapse (86% vs. 89%, $p = .33$ [Figure 1A] and 85% for ER/PR negative vs. 88% for ER/PR positive, $p = .32$, respectively [Figure 1B]) or survival (16% vs. 8%, $p = .13$ [Figure 2A] and 18% vs. 14%, $p = .42$ [Figure 2B]) at 10 years.

Table 3. Multivariable analysis for relapse, relapse-free survival, and overall survival.

Variable	Relapse			Relapse-free survival			Overall survival		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Number of prior chemotherapy regimens									
Per one increase	1.46	1.23–1.73	<.001	1.52	1.28–1.80	<.001	1.48	1.25–1.74	<.001
Disease status at transplant									
Partial remission/CR	1.43	1.10–1.87	0.008	1.34	1.04–1.74	0.025	1.34	1.03–1.75	0.029
Relapsed/refractory/CR	1.71	.75–3.90	0.2	2.03	.99–4.17	0.054	2.66	1.29–5.49	0.008
Cell source									
BM/PBSC + BM		–		2.5	1.25–4.99	0.009	2.49	1.23–5.07	0.012
PSC/PBSC + BM				1.14	.63–2.06	0.67	1.17	.63–2.17	0.62

BM = bone marrow; CI = confidence interval; CR = complete remission; HR = hazard ratio; PBSC = peripheral-blood stem cell.

The univariate prognostic factors were identified for relapse, RFS, and OS (Table 2). Gender, race, age, performance status, prior radiation therapy, hormonal status, and nodal status were not found to be prognostic factors for relapse or survival. Each additional prior chemotherapy regimen was associated with an increased risk for relapse, worse RFS, and worse OS. The disease status at time of transplant was associated with outcome: compared to patients who underwent HDC after a CR to prior therapy, patients with a partial remission had a higher risk for relapse, and experienced worse RFS and OS. Cell source (BM vs. PBSCs) was also associated with worse RFS and OS. Years since the first study transplant was also a significant variable, with improved OS per 5-year increase (Table 2).

In a multivariable analysis, additional prior chemotherapy regimens, cell source, and poor disease status at time of transplant remained prognostic for worse outcome (Table 3). Time of transplant was highly correlated with cell source (BM vs. PBSCs), and thus became nonsignificant for OS. An additional chemotherapy regimen prior to AHCT was associated with an increased risk for relapse (HR 1.5, 95% CI 1.2–1.7, $p < .001$), worse RFS (HR 1.4, 95% CI 1.2–1.6, $p < .001$), and worse survival (HR 1.4, 95% CI 1.2–1.6, $p < .001$). There was an increased risk of relapse (HR 1.4, 95% CI 1.1–1.9, $p = .008$), worse RFS (HR 1.5, 95% CI 1.1–1.9, $p = .003$), and worse OS (HR 1.5, 95% CI 1.1–1.9, $p = .004$) in the patients who had a PR compared to CR prior to transplant. The patients with relapsed or refractory disease had worse RFS and OS (HR 2.1, 95% CI 1.0–4.4, $p = .038$ and HR 2.7, 95% CI 1.3–5.4, $p = .008$, respectively), but increased risk for relapse was not significant, $p = .20$. Data regarding number and type of metastatic sites were not available for the entire cohort, and thus could not be included in the analysis.

Of the 34 long-term survivors identified, sufficient data from the medical record were available on 28 patients (Table 4). In this cohort of long-term survivors, 10 patients had metastatic disease at presentation, while 18 patients had recurrent metastatic disease. Of the 10 patients with primary metastatic disease, four patients had oligometastatic involvement of the ipsilateral supraclavicular lymph node, which would now be classified as stage IIIC disease by the current American Joint Committee on Cancer staging guidelines. Three patients had limited bone disease and three had oligometastatic disease that had been resected prior to HDC and AHCT. Of the 18 patients with recurrent metastatic disease, nine had local recurrence at the site of the incision or chest wall, and six had a single site of recurrence primarily in the lung or locoregional lymph nodes, also classified as primarily oligometastatic disease. Most of these lesions were surgically resected prior to HDC and AHCT. Of the remaining three patients, one had recurrent lesions in the liver, one had bilateral breast recurrence, and one had recurrence in the lung with

Table 4. Patient characteristics among long-term survivors.

Patient	Age	ER/PR status	Site of metastatic disease
1	36	Positive	Primary metastatic disease involving bone marrow
2	44	Positive	Recurrent liver lesion
3	29	Positive	Recurrent axillary and intramammary lymph nodes
4	48	Positive	Recurrent single lung nodule
5	38	Negative	Recurrent supraclavicular lymph node
6	42	Unknown	Recurrent single hilar mass
7	51	Unknown	Recurrent single lung nodule
8	43	Negative	Recurrent infraclavicular lymph node
9	38	Negative	Recurrent supraclavicular lymph node
10	39	Positive	Recurrent chest-wall lesion
11	44	Positive	Recurrent lesion at primary site
12	42	Positive	Recurrent chest-wall lesion
13	41	Unknown	Recurrent chest-wall lesion
14	45	Negative	Recurrent lesion at primary site and supraclavicular lymph node
15	48	Positive	Recurrent local axillary lymph node
16	44	Positive	Recurrent lesion at incision site
17	39	Negative	Recurrent chest-wall lesion
18	43	Negative	Recurrent lesion at incision site and locally
19	32	Positive	Recurrent bilateral breast lesions
20	42	Negative	Primary metastatic disease to the supraclavicular lymph node
21	44	Unknown	Primary metastatic disease to the supraclavicular lymph node
22	48	Negative	Primary metastatic disease to the supraclavicular lymph node
23	48	Unknown	Primary metastatic disease to the supraclavicular lymph node
24	44	Unknown	Primary metastatic disease to the ovary (single site)
25	53	Positive	Primary metastatic disease to solitary lung nodule
26	59	Negative	Primary metastatic disease to solitary lung nodule
27	44	Positive	Primary metastatic disease involving bone marrow
28	37	Positive	Primary metastatic disease to thoracic spine (T9) and rib

additional possible bone involvement. All patients for which data were available received systemic chemotherapy (Cy, Adriamycin, and 5-fluorouracil; Cy, methotrexate, and 5-fluorouracil; or Adriamycin and Cy) prior to HDC and AHCT. Long-term survival was not associated with age or hormonal status. The median age was 43 years (range: 29–59 years), and 13 patients were ER/PR positive, eight patients were ER/PR negative, and hormonal status was unknown in seven patients.

DISCUSSION

While the use of HDC and AHCT has largely been abandoned in the United States, several recent long-term follow-up studies, such as this one, question its role for select populations.[13–15] A recently published registry study of 415 patients from the Italian Group of Bone Marrow and Hematopoietic Stem Cell Transplantation and Cellular Therapy demonstrated a significant group (32%) of patients surviving

10 years,[15] suggesting a role for HDC and AHCT in delaying disease progression and potentially curing a subset of patients with MBC. Our current retrospective evaluation of patients who underwent HDC and AHCT for MBC at our institution also demonstrates long-term survival in a small subset of MBC patients, which we found to be predominantly those with primary or recurrent oligometastatic disease.

Our current study has several limitations, including the retrospective nature of the analysis and the limited registry data available on the patients. HER2 status was unavailable on the majority of patients, and we were unable to accurately assess the extent of metastatic disease in the entire cohort given the limited medical records. Our analysis is also subject to bias in patient selection and staging similar to previous studies. A portion of our long-term survivors were found to have supraclavicular nodal metastasis, which has previously been shown to have significantly better outcomes compared to patients with other metastatic disease, with survival similar to that of IIIB, and thus has been reclassified as stage IIIC since 2002.[16,17] Despite this, similar to past studies, we show in this current analysis a longer-than-expected long-term survival in a subset of patients, regardless of age or hormonal status in MBC. However, these long-term survivors were predominantly patients with primary or recurrent oligometastatic breast cancer.

Previous studies have suggested that oligometastatic breast cancer is a distinct subgroup with long-term prognosis that is superior to MBC.[18–20] Oligometastatic breast cancer comprises about 1–10% of newly diagnosed MBC patients, and is potentially curable.[18,21] While patients with MBC are generally defined by chemosensitivity, the improved prognosis of oligometastatic disease is distinct due to the low-tumor burden at the time of metastatic recurrence. The role for systemic therapy, however, is underscored by the fact that all patients with oligometastatic disease treated with local therapy alone will inevitably die from disease progression due to micrometastatic disease.

Data on the use of HDC and AHCT as adjuvant therapy after local treatment for oligometastatic breast cancer are limited and have only been evaluated in one prospective trial evaluating 60 patients.[19] The trial included patients with limited bone metastases, but excluded patients with brain and liver metastases. At 5 years, RFS and OS were 52% and 62%, respectively. HER2 overexpression, number of metastatic sites, and increased axillary nodal ratio were found to be important prognostic factors for worse outcome, and a prognostic model for risk of relapse after AHCT was proposed for this oligometastatic population.

A series of consecutive trials,[22–24] the majority of which had locoregional recurrence alone, evaluated standard-dose anthracycline-based and docetaxel-based adjuvant chemotherapy for systemic treatment of single-site metastases. In the three anthracycline-based trials, 20-year disease-free survival (DFS) and OS reached 26%, while in the docetaxel-based trial, 5-year DFS and OS were 34% and 59%, respectively. Compared with historical controls of patients who did not receive chemotherapy after local therapy, patients at the same institution who did not receive systemic treatment had significantly worse outcomes with a 15-year DFS rate of only 3%. This underscores the fact that systemic chemotherapy remains a critical component to the successful control of microscopic diseases and a key to a potential cure in patients with oligometastatic breast cancer.

The long-term survival after HDC and AHCT for MBC is still rare, and there remains no demonstrable benefit to transplant. The 10–15% of long-term survivors seen in this study represent a population of primarily oligometastatic or a locally recurrent disease, which may otherwise be curable with other multimodality therapies.

CONFLICTS OF INTEREST

The authors of this study have no relevant conflicts of interest to disclose.

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