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ORIGINAL ARTICLE

Allogeneic hematopoietic cell transplantation for metastatic breast cancer

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We reviewed 66 women with poor-risk metastatic breast cancer from 15 centers to describe the efficacy of allogeneic hematopoietic cell transplantation (HCT). Median follow-up for survivors was 40 months (range, 3–64). A total of 39 patients (59%) received myeloablative and 27 (41%) reduced-intensity conditioning (RIC) regimens. More patients in the RIC group had poor pretransplant performance status (63 vs 26%, $P = 0.002$). RIC group developed less chronic GVHD (8 vs 36% at 1 year, $P = 0.003$). Treatment-related mortality rates were lower with RIC (7 vs 29% at 100 days, $P = 0.03$). A total of 9 of 33 patients (27%) who underwent immune manipulation for persistent or progressive disease had disease control, suggesting a graft-vs-tumor (GVT) effect. Progression-free survival (PFS) at 1 year was 23% with myeloablative conditioning and 8% with RIC ($P = 0.09$). Women who developed acute GVHD after an RIC regimen had lower risks of relapse or progression than those who did not (relative risk, 3.05: $P = 0.03$), consistent with a GVT effect, but this did not affect PFS. These findings support the need for preclinical and clinical studies that facilitate targeted adoptive immunotherapy for breast cancer to explore the benefit of a GVT effect in breast cancer.

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Introduction

Management of metastatic breast cancer remains a challenge despite advances in treatment and better understanding of the biological and molecular basis of the disease during the past two decades. Use of high-dose chemotherapy for metastatic breast cancer, first proposed in the 1980s, was based on dose–response concepts.[1,2] Autologous hematopoietic cell transplantation (HCT) was used to rescue the bone marrow from the myelotoxic effects of high-dose chemotherapy. Of eight randomized phase III studies comparing conventional chemotherapy with autologous HCT,[3–11] seven suggested that high-dose therapy leads to improved progression-free or event-free survival; however, none of these seven studies have been published in the peer-reviewed literature.[3–5,8–11] One published phase III trial showed no advantage of autologous HCT over conventional therapy in terms of either progression-free survival (PFS) or overall survival.[6,7] Disease recurrence remained a major problem even among those who initially achieved a complete response to high-dose therapy. Incomplete disease eradication or contamination of the autologous stem-cell product by malignant cells may contribute to disease recurrence.

Allogeneic HCT for metastatic breast cancer has two potential advantages over autologous HCT—a cancer-free graft and immune-mediated graft-vs-tumor (GVT) effects from the donor's cells. GVT effects against leukemias and lymphomas are well established.[12–17] In the 1980s, spontaneous GVT effects against solid tumors after allogeneic HCT, even with reduced-intensity conditioning (RIC) regimens, were documented in murine models.[18] Since the first small studies were published in the 1990s,[19–23] interest has increased in harnessing the potentially beneficial GVT effects of allogeneic HCT for the treatment of metastatic breast cancer.

To avoid the high treatment-related morbidity and mortality associated with the use of traditional myeloablative

conditioning, RIC regimens, with or without the use of donor lymphocyte infusion (DLI) after the transplant were developed.[24–28] With RIC regimens, the goal is the induction of immune GVT effects rather than chemotherapy-mediated cytoreduction. Clinical responses suggesting a GVT effect have been described, but none of the studies have included more than 20 patients with metastatic breast cancer. We analyzed the outcomes of patients given allogeneic HCT for treatment of metastatic breast cancer reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) or the European Group for Blood and Marrow Transplantation (EBMT). The objectives were to describe the features and outcomes of these patients, to compare toxicity and outcome after traditional myeloablative conditioning vs RIC and to explore whether allogeneic HCT induces a GVT effect.

Patients and methods

Center for International Blood and Marrow Transplant Research

The CIBMTR is a voluntary working group of more than 500 transplantation centers worldwide that contribute detailed data on consecutive HCTs to the Statistical Center at the Medical College of Wisconsin in Milwaukee. Participating centers are required to register all transplantations consecutively; compliance is monitored by on-site audits. Patients are followed longitudinally, with yearly follow-up.

The CIBMTR collects data at two levels: Registration and Research. Registration data include disease type, age, sex, pretransplant disease stage and chemotherapy-responsiveness, date of diagnosis, graft type (bone marrow- and/or blood-derived stem cells), high-dose conditioning regimen, post-transplant disease progression and survival, development of a new malignancy and cause of death. Research data are collected on subsets of registered patients and include comprehensive pre- and post-transplant clinical information.

European Group for Blood and Marrow Transplantation

The EBMT was founded in 1974 and consists of more than 400 transplant groups in Europe and other countries reporting all their HCTs by the Med A form, similar to the registration form used by CIBMTR. The completeness of reporting is checked by an annual survey and site visits. The EBMT is composed of 21 Working Parties each focusing on major disease groups or HCT complications. All patients with metastatic breast cancer registered with the allogeneic HCT subcommittee of the Solid Tumors Working Party for transplants performed between 1992 and 2000 were included in this study. The data for this study were obtained by collecting Med A information and additional disease-specific information.

For this study, the CIBMTR and EBMT centers also completed supplemental data forms regarding the withdrawal of immunosuppression or DLI and response (if any) to these maneuvers. Data were reviewed to eliminate overlapping reporting of patients between CIBMTR and EBMT teams.

Patients

All women who underwent an allogeneic transplant for metastatic breast cancer between 1992 and 2000 and for whom comprehensive data collection forms were submitted to the CIBMTR or to the Allogeneic HCT Subcommittee of the Solid Tumors Working Party of the EBMT were included. Demographic characteristics and survival of the study population were similar to all allogeneic HCT recipients with metastatic breast cancer registered with the CIBMTR during the same time period.

Patients who had had prior autologous HCT were included, except for patients who underwent a planned sequential autologous-allogeneic approach. Patients who received a planned sequential autologous-allogeneic HCT were excluded. Information on patients who received such a tandem HCT approach was recently reported.[29]

Conditioning regimens

The conditioning regimens used in allogeneic HCT for metastatic breast cancer were divided into myeloablative group and RIC group. The criteria of the division were based on the dose of chemotherapeutic agent in each regimen suggested by the second EBMT workshop.[30]

End points

The end points in this study were transplant-related mortality (TRM), breast cancer progression or relapse, PFS and overall survival. Acute and chronic GVHD and tumor response to immune manipulation after transplantation were described. TRM was defined as death without progression of breast cancer; relapse or progression were treated as competing events. Disease progression was defined as clinical recurrence (after a complete response) or progression of disease at any site, as determined by the treating physician at the transplant center. Because patients who had a transplant during the study period had been evaluated for radiographic disease response before the RECIST criteria were in common use, all responses represent the traditional World Health Organization criteria.[31] For analyses of PFS, treatment failures were defined as clinical disease relapse or progression at any site or death from any cause; data on patients who were alive and without disease progression were censored at the time of last follow-up. For analyses of overall survival, failure was death from any cause; data were censored at last follow-up for surviving patients.

Statistical analysis

Patient-, disease- and transplant-related characteristics of patients in the myeloablative and RIC cohorts were compared by using the χ^2-test for categorical variables and the Kruskal–Wallis test for continuous variables. Univariate probabilities of overall survival and PFS were calculated by using Kaplan–Meier estimates; the log rank test was used for univariate comparisons. Probabilities of acute and chronic GVHD, TRM and disease relapse or

progression were calculated by using cumulative incidence estimates to accommodate competing risks.[32] TRM and disease relapse (or progression) were treated as competing events. Patients who received DLI were censored for incidence of GVHD at the date of DLI.

Because the number of patients was relatively small, analyses were limited to comparison of outcomes in the presence or absence of GVHD with adjustment for conditioning intensity. Cox proportional hazards regression was used to examine whether acute or chronic GVHD and DLI affected outcomes. We used a time-dependent covariate to model the potential effects of GVHD or DLI, in which patients were considered as having GVHD or DLI only after the onset time of GVHD or after the date of receiving DLI, respectively. Time to development of acute GVHD and any GVHD were each tested in the models, with nearly identical results. Because nearly all patients who developed chronic GVHD had preceding acute GVHD, we chose to present results for acute GVHD. The assumption of proportional hazards regression was tested by using a time-dependent covariate. Interactions between myeloablative vs RIC and covariate factors were tested with the likelihood ratio test.

Results

Patient characteristics

Data were provided from 15 transplant centers for 66 women who received allogeneic HCT for metastatic breast cancer between 1992 and 2000 (Table 1). Median follow-up time for survivors was 40 months (range, 3–64 months). Median patient age at the time of transplantation was 41 years (range, 25–60 years). Slightly less than half of the patients (41%) had a Karnofsky performance score of less than 80 before transplantation. A total of 37 patients (56%) had hormone-receptor–positive disease; information on HER-2/*neu* status was not available. A total of 31 patients (47%) had responsive disease before HCT; 17 patients (26%) had progressive disease before transplantation. The median number of prior regimens (not including autologous HCT) was 2 (range, 1–6). The median number of sites of metastatic disease at the time of transplantation was 2 (range, 0–5). A total of 17 patients (26%) had undergone prior autologous HCT. Traditional myeloablative conditioning regimens were used for 39 patients (59%) and RIC regimens for 27 patients (41%). Most patients received transplants from an HLA-identical sibling; two received cells from an unrelated donor. Peripheral blood stem cells were used for 92% of the patients. Prophylaxis for GVHD is shown in Table 1. Patient and disease characteristics were similar between these two groups (Table 1) except for Karnofsky score ($\geqslant 80$ in 74% of the myeloablative group vs only 37% in the RIC group) and having had one or more prior autologous transplants (8% of the myeloablative group vs 52% of the RIC group).

Graft-vs-host disease and immune manipulation

The cumulative incidence of grade II-IV acute GVHD at 100 days was 44% after myeloablative conditioning and 34% after RIC (Table 2). The cumulative incidence of chronic GVHD at 1 year was much higher in the myeloablative group (36%) than in the RIC group (8%) (Table 2). Chimerism data were not available to confirm long-term engraftment in the RIC group. A total of 33 patients (50%) received additional immune manipulation (withdrawal of immunosuppression, administration of DLI or both) for disease control within 60 days after transplantation. Six patients (18%) had significant disease response and three other patients (9%) had minor response or stable disease (Table 3).

Survival, treatment-related mortality, response and relapse

Overall survival rates after myeloablative conditioning were 51% at 1 year and 25% at 2 years vs 26% at 1 year and 15% at 2 years after RIC (Table 2, Figure 1). The cumulative incidence of TRM at 100 days was 26% in the myeloablative group and 7% for the RIC group (Table 2, Figure 2). Among patients not in complete response at transplantation, the overall response rate (complete or partial response) after HCT was 31% in the myeloablative group (three complete responses and nine partial responses) and 29% in the RIC group (two complete responses and six partial responses) (Table 3). A total of 6 of the 33 patients (18%) who received immune manipulation for disease control had a complete ($n=1$) or partial ($n=5$) response; 3 others (9%) had stable disease (Table 3). The cumulative incidence of disease relapse or progression in the myeloablative group was 44% at 1 year and 62% at 2 years; corresponding incidences in the RIC group were 76 and 84% (Table 2, Figure 3). Probabilities of PFS in the myeloablative group were 23% at 1 year and 5% at 2 years; corresponding probabilities of PFS in the RIC group were 8 and 0% (Table 2).

Analysis of conditioning vs graft-vs-host disease

The presence of acute GVHD was associated with a significantly increased risk of TRM ($P=0.03$) for recipients of myeloablative HCT compared to those who did not develop acute GVHD. The risk of TRM associated with aGVHD was also increased but not statistically significant for RIC recipients (Table 4). In Cox time-dependent analysis, women treated with RIC regimens who developed acute GVHD had a lower risk of progression relative to those who did not develop acute GVHD (relative risk 0.33: $P=0.03$). For patients given myeloablative regimens, no difference in risk of relapse was found between those who developed acute GVHD and those who did not. For patients who developed acute GVHD, the risk of progression was similar for women given RIC and for women given myeloablative regimens. However, for those who did not develop acute GVHD, the risk of progression in patients who received myeloablative regimens was significantly decreased compared to those received RIC regimens (relative risk 0.14: $P\leqslant 0.0001$).

Among women given a myeloablative conditioning regimen, the development of acute GVHD was associated with an increased risk of treatment failure (progression/relapse or death) (relative risk 2.04: $P=0.03$) (Table 4). In contrast, for women treated with RIC regimens, there was a

Table 1 Characteristics of patients who underwent allogeneic HCT for metastatic breast cancer according to intensity of conditioning regimen

Characteristic	*Total*, N *(%)*	*RIC group*, N *(%)*	*Myeloablative group*, N *(%)*	P-*value*[a]
Total number of patients	66 (100)	27 (100)	39 (100)	
Median age at transplantation (range)	41 years (25–60)	42 years (28–57)	41 years (25–60)	0.41
Median follow-up of survivors (range)	40 months (3–64)	18 months (3–35)	41 months (22–64)	
Year of transplant				
1992	1 (2)	0	1 (3)	
1994	3 (4)	1 (4)	2 (5)	
1995	3 (4)	0	3 (8)	
1996	8 (12)	0	8 (20)	
1997	7 (11)	0	7 (18)	
1998	19 (29)	7 (26)	12 (31)	
1999	18 (27)	12 (44)	6 (15)	
2000	7 (11)	7 (26)	0	
Karnofsky performance status at transplant				<0.002
$\geqslant 80$	39 (59)	10 (37)	29 (74)	
<80	27 (41)	17 (63)	10 (26)	
Estrogen/progesterone receptor status				0.68
Positive	37 (56)	16 (60)	21 (54)	
Negative	11 (17)	4 (15)	7 (18)	
Missing/unknown	18 (27)	7 (25)	11 (28)	
Disease status at transplant				0.13
Complete remission	6 (9)	4 (15)	2 (5)	
CRU	2 (3)	1 (4)	1 (3)	
Partial response	23 (35)	10 (37)	13 (33)	
Stable disease	18 (27)	3 (11)	15 (38)	
Progressive disease	17 (26)	9 (33)	8 (21)	
Number of prior treatments (median)[b]	2.0	3	2	0.10
1	7 (11)	2 (7)	5 (13)	
2	27 (41)	10 (37)	17 (44)	
3	14 (21)	4 (15)	10 (26)	
4	11 (17)	6 (22)	5 (13)	
5	4 (6)	2 (7)	2 (5)	
6	3 (4)	3 (11)	0	
Number of metastatic sites before conditioning (median)	2	2	2	0.34
None	8 (12)	5 (18)	3 (8)	
1	24 (36)	8 (30)	16 (41)	
2	22 (33)	12 (44)	10 (26)	
3	11 (17)	1 (4)	10 (26)	
5	1 (2)	1 (4)	0	
Location of metastases at conditioning				
Bone or bone marrow	41 (62)	14 (52)	27 (69)	0.15
Liver	30 (45)	10 (37)	20 (51)	0.25
Lung	14 (21)	8 (30)	6 (15)	0.16
Number of prior transplants				<0.001
None	49 (74)	13 (48)	36 (92)	
One	14 (21)	11 (41)	3 (8)	
Two	3 (5)	3 (11)	0	
Myeloablative conditioning regimens				
Cyclophosphamide/BCNU/thiotepa			22 (56)	
Cyclophosphamide/carboplatin/thiotepa			7 (18)	
Melphalan/busulfan			5 (13)	
Stamp V			2 (5)	
Carboplatin/thiotepa			1 (2)	
Busulfan/cyclophosphamide			1 (2)	
Busulfan/cyclophosphamide/thiotepa			1 (2)	
Reduced-intensity conditioning regimens				
Fludarabine/cyclophosphamide ± thiotepa		9 (33)		
Cyclophosphamide/cisplatin based		5 (19)		
Fludarabine/busulfan ± ATG		4 (15)		
Total body irradiation 200 cGy		3 (11)		

Table 1 Continued

Characteristic	*Total,* N *(%)*	*RIC group,* N *(%)*	*Myeloablative group,* N *(%)*	P-*value*[a]
Fludarabine/melphalan ± ATG		2 (7)		
Fludarabine/thiotepa ± ATG		2 (7)		
Carboplatin/etoposide/Ifosfamide		1 (4)		
Mitoxantrone/melphalan/ATG		1 (4)		
Graft source				0.23
HLA identical sibling	64 (97)	27 (100)	37 (95)	
Unrelated	2 (3)	0	2 (5)	
Graft type				0.32
Peripheral blood stem cells	61 (92)	26 (96)	35 (90)	
Bone marrow	5 (8)	1 (4)	4 (10)	
GVHD prophylaxis				0.001
CSA ± steroids	14 (22)	7 (29)	7 (18)	
Tacrolimus/MTX	21 (33)	1 (4)	20 (51)	
CSA/MTX ± steroids	11 (17)	8 (33)	3 (8)	
T-cell depletion ± CSA	6 (9)	5 (21)	1 (2)	
None	3 (5)	3 (12)	0 (0)	
Tacrolimus only	2 (3)	0 (0)	2 (5)	
Other/unknown	9 (14)	3 (8)	6 (15)	
Immune manipulation for residual or progressive disease at 60 days	33 (50)	14 (56)	19 (49)	
Immune withdrawal	29 (44)	13 (48)	16 (41)	
DLI	21 (32)	12 (44)	9 (23)	

Abbreviations: ATG = anti-thymocyte globulin; BCNU = 1,3-bis(2-chloroethyl)-1-nitrosourea; CRU = complete response except for bone scan abnormalities of unknown significance; CSA = cyclosporine A; DLI = donor lymphocyte infusion; MTX = methotrexate; RIC = reduced-intensity conditioning; STAMP V = cyclophosphamide, thiotepa and carboplatin.
[a]Comparing RIC with myeloablative group.
[b]Excluding autologous stem-cell transplant.

Table 2 Estimated probabilities of treatment-related mortality, disease relapse or progression, progression-free survival, overall survival and acute and chronic GVHD after allogeneic HCT for metastatic breast cancer

	N	*100 day (95% CI)*	*180 days (95% CI)*	*1 year (95% CI)*	*2 years (95% CI)*	*3 years (95% CI)*
Overall survival	66			42% (30–54%)	21% (12–32%)	15% (7–25%)
Myeloablative	39			51% (36–67%)	25% (13–40%)	19% (8–33%)
RIC	27			26% (11–45%)	15% (3–34%)	7% (<1–25%)
				($P = 0.04$)	($P = 0.33$)	($P = 0.21$)
Treatment-related mortality[a]						
Myeloablative	39	26% (13–40%)		33% (20–48%)	33% (20–48%)	
RIC	27	7% (1–19%)		16% (5–30%)	16% (5–30%)	
		($P = 0.03$)		($P = 0.07$)	($P = 0.07$)	
Relapse/progression[a]						
Myeloablative	39			44% (29–59%)	62% (47–75%)	
RIC	27			76% (59–89%)	84% (70–95%)	
				($P = 0.003$)	($P = 0.02$)	
Progression-free survival						
Myeloablative	39			23% (11–37%)	5% (1–14%)	
RIC	27			8% (1–22%)	0%	
				($P = 0.09$)	—	
Acute GVHD[a]						
Myeloablative	39	44% (29–59%)	44% (29–59%)			
RIC	26	35% (18–53%)	35% (18–53%)			
		($P = 0.45$)	($P = 0.45$)			
Chronic GVHD[a]						
Myeloablative	39		15% (6–28%)	36% (22–51%)	36% (22–51%)	
RIC	26		8% (l–22%)	8% (1–22%)	8% (1–22%)	
			($P = 0.36$)	($P = 0.003$)	($P = 0.001$)	

Abbreviations: CI = confidence interval; HCT = hematopoietic cell transplantation; RIC = reduced intensity conditioning.
[a]Calculated using cumulative incidence.
P-values in all columns represent comparison of myeloablative group to the RIC group.

Table 3 Response rates after allogeneic HCT for metastatic breast cancer

	Total, N *(%)*	*RIC group*, N *(%)*	*Myeloablative group*, N *(%)*
Total number of patients	66 (100)	27 (100)	39 (100)
Overall response to transplant[a]			
Complete response		2 (7)	3 (8)
Partial response		6 (22)	9 (23)
Response to early immune withdrawal or DLI	33 (100)		
Complete response	1 (3)		
Partial response	5 (15)		
Minor response or stable disease	3 (9)		
Disease progression	22 (67)		
Unknown	2 (6)		

Abbreviations: DLI = donor lymphocyte infusion; HCT = hematopoietic cell transplantation; RIC = reduced intensity conditioning.
[a]Among patients who were not in complete remission before transplant.
$P = 0.92$ comparing RIC group to myeloablative group.

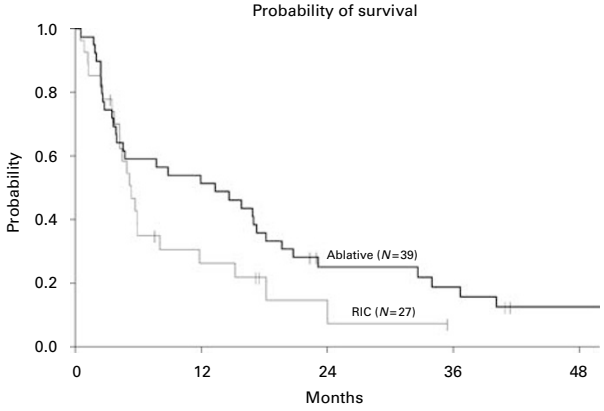


Figure 1 Overall survival for patients with metastatic breast cancer who underwent allogeneic hematopoietic cell transplantation, stratified by treatment approach.

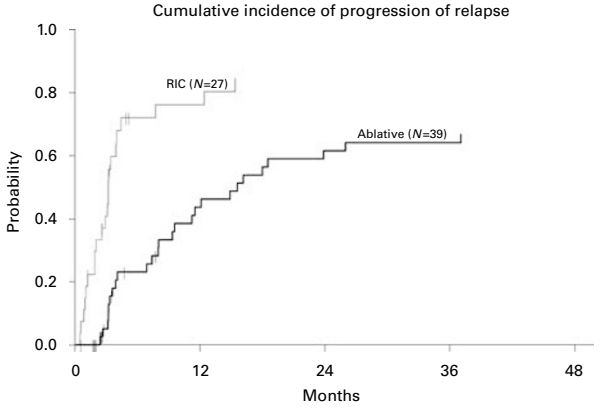


Figure 3 Cumulative incidence of progression or relapse for patients with metastatic breast cancer who underwent allogeneic hematopoietic cell transplantation.

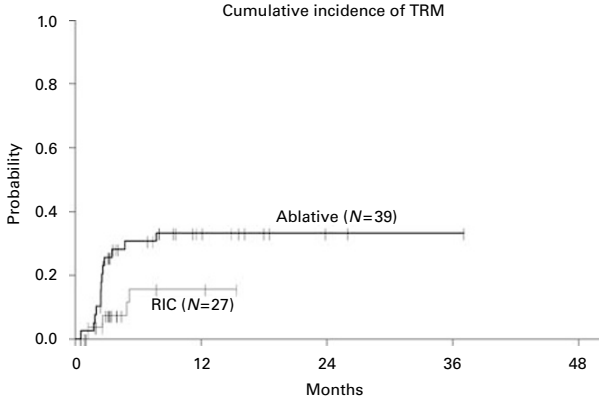


Figure 2 Cumulative incidence of treatment-related mortality for patients with metastatic breast cancer who underwent allogeneic hematopoietic cell transplantation.

decreased risk of treatment failure associated with development of acute GVHD (relative risk 0.51: $P = 0.12$). This risk was not, however, statistically significant. As was true in the models for relapse, no significant difference in the risk of treatment failure was found between myeloablative and RIC approaches when acute GVHD developed, but for patients who did not develop acute GVHD, those who received myeloablative regimens had less treatment failure than those received RIC regimens. Neither GVHD nor intensity of conditioning was associated with overall survival in bivariate analysis.

Discussion

Published clinical studies have suggested that allogeneic HCT can produce a GVT effect in metastatic breast cancer.[24–28] However, those studies included very small numbers of patients. This retrospective registry study suggests that allogeneic HCT can produce a GVT effect in metastatic breast cancer, as evidenced by tumor response after post-transplant immune manipulation and the association of acute GVHD with reduced risk of disease progression. These findings are consistent with a graft-vs-malignancy effect in hematologic malignancies.

The most direct evidence of the existence of a GVT effect is disease response associated with immune manipulations such as DLI.[28] In this study, nine patients (27%) who underwent additional immune manipulation after

Table 4 Bivariate analyses of conditioning and GVHD[a] on treatment-related mortality, disease relapse or progression and progression-free survival after allogeneic HCT for metastatic breast cancer

Variable	*Relative risk of treatment-related mortality (95% CI)*	P-*value*	*Relative risk of progression (95% CI)*	P-*value*	*Relative risk of treatment failure*[b] *(95% CI)*	P-*value*
Myeloablative conditioning Yes vs no acute GVHD	3.61 (1.10–11.87)	0.03	1.46 (0.63–3.40)	0.38	2.04 (1.05–3.96)	0.03
RIC Yes vs no acute GVHD	1.53 (0.21–11.24)	0.67	0.33 (0.12–0.88)	0.03	0.51 (0.21–1.20)	0.12
No GVHD Myeloablative vs RIC	0.87 (0.16–4.91)	0.87	0.14 (0.06–0.35)	<0.0001	0.25 (0.11–0.52)	0.0002
Yes acute GVHD Myeloablative vs RIC	2.05 (0.44–9.52)	0.35	0.64 (0.24–1.75)	0.39	0.98 (0.44–2.22)	0.98

Abbreviations: CI = confidence interval; HCT = hematopoietic cell transplantation; RIC = reduced intensity conditioning.
[a]A significant interaction was noted between the aggressiveness of the conditioning regimen and acute GVHD on the outcome.
[b]Treatment failure is the inverse of progression-free survival—patients with increased risk of treatment failure have increased risk of death or progression/relapse.

transplantation showed disease response or stable disease (Table 3).

Indirect evidence of a GVT effect comes from the observation of disease control in combination with acute GVHD when an RIC regimen was used (Table 4). Disease progression was observed more frequently among those who received RIC regimens and did not develop acute GVHD compared to those patients who received RIC regimens and developed acute GVHD. For women treated with conventional high-dose conditioning, those who developed acute GVHD were at significantly higher risk of TRM and did not experience better disease control than women without acute GVHD. This suggests that an immune-mediated GVT effect associated with acute GVHD in patients given RIC regimens played a role in disease control. The effect of GVHD on recurrence may represent a minor antigen specific alloimmune effect rather than a tumor-specific response for breast cancer. Further research with larger numbers of patients is required to determine whether GVT effect occurs without GVHD or if it could be separated in a clinically meaningful fashion from GVHD.

One explanation for the above findings is that most of the patients (79%) in the myeloablative group had stable or responsive disease before transplantation, and they also had had fewer prior treatments (median, 2) than did the patients in the RIC group, though these differences were not statistically significant. This suggests that most of the patients in the myeloablative group had relatively chemosensitive disease. Therefore, the immune-mediated GVT effect may not play a major role in decreasing risk of progression in patients with relatively chemosensitive disease who received myeloablative regimens. However, the increased TRM in the myeloablative group may offset the benefit associated with development of GVHD. Therefore, development of acute GVHD was associated with increased treatment failure among those who received a myeloablative regimen.

There are several limitations of this study. First is the heterogeneity of the patient and disease characteristics and transplant approaches. Many patients had poor performance status and nonresponsive disease before the transplant. One fourth of the patients had prior autologous HCT that failed, and at least half had visceral organ involvement. The types of conditioning regimens and GVHD prophylaxis, and the timing and intent of immune manipulation varied across transplant centers. This heterogeneity reflects variation in the eligibility criteria among the different transplant centers and the selection of patients with poor prognosis typical of early investigational studies of high-risk procedures. Although a few characteristics were statistically significantly different between the conditioning approaches (RIC vs ablative), small numbers limited our ability to further adjust for the effects of patient, disease and transplant characteristics on transplant outcome. Data were not available regarding HER-2 expression in these patients. Data were collected from multiple sources, and data regarding tumor responses were not subjected to review outside of the transplant center performing the procedures.

Despite these limitations, our analysis reveals some interesting findings. Our analysis supports an allogeneic GVT effect in metastatic breast cancer that could produce disease response. Whether this can be separated from GVHD is to be determined in future studies. A second finding is the demonstration that the TRM associated with allogeneic HCT when an RIC regimen was used was much lower than the TRM associated with traditional myeloablative regimens. However, more intense conditioning regimens may improve disease control, as shown by the lower relapse or progression rates among patients given myeloablative therapy as compared with those given reduced-intensity therapy.

In murine models, a GVT effect was demonstrated in mice implanted with 4T1 mammary carcinoma cell line and given minor histocompatibility-mismatched DBA/2 spleen cells.[33] This direct GVT effect mediated by the alloreactive donor splenocytes in the absence of any anti-carcinoma agents has also been demonstrated by direct inhibition of liver metastases through intraportal inoculation of allogeneic splenocytes but not syngeneic splenocytes.[34] Activated allogeneic natural killer splenocytes and allogeneic donor-specific CD8+ cytotoxic T cells with a type 2 cytokine phenotype have also been shown induce a GVT

effect against metastatic mammary carcinoma.[35,36] The same murine models of metastatic mammary carcinoma have demonstrated as an effective immunotherapy of metastatic mammary carcinoma by allogeneic HCT after non-myeloablative conditioning.[37] Despite these findings, more preclinical studies should be conducted to facilitate targeted adoptive immunotherapy for breast cancer. These studies need to clarify the nature of the GVT effect, including identification of the specific tumor antigens involved in GVT (if any) and identification of methods to promote GVT without GVHD.

In summary, more preclinical studies will result in deployment of innovative allotransplant approaches that take advantage of GVT effects to control disease while minimizing TRM or development of GVHD. Future studies should only include patients with better performance status and with chemotherapy responsive disease before transplant who may be more likely to benefit from GVT effects. One recent approach is the use of planned tandem autologous/allogeneic RIC transplantation for patients with metastatic breast cancer.[29]

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Appendix

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