Biol Blood Marrow Transplant 19 (2013) 602–606

Outcomes of Related Donor HLA-Identical or HLA-Haploidentical Allogeneic Blood or Marrow Transplantation for Peripheral T Cell Lymphoma

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Article history:
Received 13 September 2012
Accepted 11 January 2013

Key Words:
Peripheral T-cell lymphoma
Allogeneic blood or marrow transplantation
Haploidentical
Reduced-intensity conditioning
Survival outcomes

A B S T R A C T

The role of allogeneic blood or marrow transplantation (alloBMT) for peripheral T cell lymphoma (PTCL) remains to be defined. There is growing interest in reduced-intensity conditioning (RIC) regimens and/or utilization of human leukocyte antigen haploidentical (haplo) grafts given concerns about treatment-associated toxicities and donor availability. We reviewed the outcomes of 44 consecutive, related donor alloBMTs for PTCL performed at Johns Hopkins Hospital from 1994 to 2011, including 18 RIC/haplo alloBMTs. Patients receiving RIC (n = 24) were older, with median age of 59 years (range, 24 to 70), than patients receiving myeloablative conditioning (MAC, n = 20), with median age of 46 years (range, 18 to 64), $P = .01$. The median age at RIC/haplo alloBMT was 60 years. The estimated 2-year progression-free survival (PFS) was 40% (95% confidence interval [CI], 26% to 55%) and overall survival (OS) was 43% (95% CI, 28% to 59%). In older patients (≥60, n = 14), the estimated 2-year PFS and OS were 38% (95% CI, 18% to 79%) and 45% (95% CI, 24% to 86%), respectively. On unadjusted analysis, there was a tendency toward superior outcomes for alloBMT in first remission versus beyond first remission, with an estimated 2-year PFS of 53% (95% CI, 33% to 77%) versus 29% (95% CI, 9% to 45%), $P = .08$. On competing risk analysis, the 1-year cumulative incidence of relapse was 38% for MAC/HLA-identical alloBMTs and 34% for RIC/haplo alloBMTs. Estimated 1-year nonrelapse mortality was 10% for MAC and 8% for RIC (11% for RIC/haplo alloBMT). On unadjusted landmark analysis, patients with acute grade II-IV or chronic graft-versus-host disease (GVHD) had a 17% probability of relapse (95% CI, 0% to 39%), compared with 66% (95% CI, 48% to 84%) in patients without GVHD, $P = .04$. Utilization of RIC and alternative donors expands treatment options in PTCL to those who are older and unable to tolerate high-dose conditioning, with outcomes comparable with approaches using myeloablative regimens and HLA-matched donors. AlloBMT may be appropriate in first remission in select high-risk cases.

INTRODUCTION

Peripheral T cell lymphomas (PTCLs) have variable responses to chemotherapy and often relapse, even after high-dose therapy with autologous stem cell rescue [1-4]. Thus, there is growing interest in allogeneic blood or marrow transplantation (alloBMT) as an alternative given its potential for a graft-versus-lymphoma (GVL) effect [5-9]. Older patient age, difficulty identifying human leukocyte antigen (HLA)-identical donors, and concerns about transplant-related toxicities have limited the exploration of this approach. Yet, recent advances in alloBMT platforms, including high-dose post-transplantation cyclophosphamide for graft-versus-host disease (GVHD) prophylaxis, have significantly reduced the morbidity of alloBMT, including HLA-haploidentical (haplo) alloBMT [10,11]. Herein, we report the Johns Hopkins Hospital outcomes of related donor alloBMT for PTCL, half of which used haplo grafts.

METHODS

Patients

After institutional review board approval, the Johns Hopkins BMT registry was screened for diagnoses of PTCL or natural killer (NK) cell lymphoma. Forty-four consecutive alloBMTs for PTCL in adults were identified from January 1994 to June 2011 and selected for analysis. Diagnostic pathology was centrally reviewed before alloBMT. For the purposes of this article, histologic diagnoses were designated using the 2008 World Health Organization classification of mature T cell and NK cell neoplasms [12]. International Prognostic Index or Prognostic Index for T cell lymphoma scores could not be tabulated for many of the patients due to missing data from the time of PTCL diagnosis and are thus not available for this alloBMT cohort.

The presence of high-risk disease features as well as a strong institutional research focus on alternative donor transplantation factored into decisions regarding autologous BMT versus alloBMT, with 80% of patients in this cohort enrolled in an alloBMT clinical trial. The decision to take a patient to alloBMT in first remission was dependent on the treating physician and was based in part on the patient's candidacy for myeloablative conditioning (MAC), with in reduced-intensity conditioning (RIC)/haplo alloBMT prioritized over autologous BMT for those unable to tolerate MAC.

Transplantation

MAC regimens included Bu/Cy (busulfan pharmacokinetically dosed in 16 doses over 4 days to achieve an area under the curve of 800 to 1400 mmol × min/L and cyclophosphamide 50 mg/kg i.v. daily for 4 days), Cy/TBI (cyclophosphamide 50 mg/kg i.v. daily for 4 days and 1200 cGy total body irradiation given as 300 cGy per day for 4 days), or Bu/Flu (busulfan pharmacokinetically dosed as above and fludarabine 40 mg/mm i.v. daily for 4 days). RIC regimens were fludarabine-based, either Flu/Cy/TBI (fludarabine

Financial disclosure: See Acknowledgments on page 606.

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1083-8791/$ – see front matter © 2013 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.01.006

30 mg/mm i.v. daily for 5 days, cyclophosphamide 14.5 mg/kg i.v. daily for 2 days, and 200 cGy TBI) or Flu/TBI. Supportive care measures were according to Johns Hopkins Hospital institutional standards.

Through 2006, cyclosporine was used for GVHD prophylaxis for all MAC alloBMTs. After 2006, PT/Cy (post-transplantation cyclophosphamide 50 mg/kg i.v. on days 3 and 4 after alloBMT) was used as sole GVHD prophylaxis for MAC/HLA-identical alloBMTs. For RIC/HLA-identical alloBMTs, the GVHD prophylaxis regimen was PT/Cy (days 3 and 4) with mycophenolate mofetil 15 mg/kg orally three times daily up to 1000 mg/dose given days 4 to 33 after transplantation. For RIC/haplo alloBMTs, the GVHD prophylaxis regimen was PT/Cy (days 3 and 4), tacrolimus, and mycophenolate mofetil (days 5 to 35). In the absence of GVHD, tacrolimus was continued with goal trough of 5 to 15 ng/mL until day 180 after transplantation.

Definitions of Disease Status and Clinical Outcomes

Primary induction failure (PIF) was defined as progressive disease during first-line treatment or disease relapse within 2 months of treatment completion. Chemoresistant disease was designated in patients with primary induction failure or relapse refractory to salvage chemotherapy. Disease status at the time of alloBMT was determined in accord with standard response criteria for non-Hodgkin lymphoma [13].

Neutrophil recovery time was the number of days from alloBMT to the first of 3 consecutive days with an absolute neutrophil count above 500/μL. Platelet recovery time was the number of days from alloBMT to the first day with a platelet count of ≥20,000 without platelet transfusion in the preceding week. Donor chimerism was determined by restriction fragment length polymorphisms or polymerase chain reaction of variable nucleotide tandem repeats. Full donor chimerism was defined as achievement of ≥95% donor T cells in the blood at post-transplant day 30 or in the blood or bone marrow at post-transplant day 60. Mixed chimerism was defined as 5% to 94% donor cells. Primary graft failure was defined as <5% donor cells by posttransplant day 60. Day 60 engraftment was determined by donor chimerism, if available, or count recovery criteria. Acute GVHD was graded per the Keystone criteria, and chronic GVHD was graded per the 2005 National Institutes of Health Working Group Report and Seattle standard guidelines [14-16].

Progression-free survival (PFS) was the time from alloBMT to disease relapse, progression, or death from any cause. Overall survival (OS) was the time from alloBMT to death from any cause. Nonrelapse mortality (NRM) was defined as death without disease relapse.

Statistics

The dataset was locked for analysis on December 20, 2011. Descriptive statistics were used to summarize baseline patient and alloBMT characteristics and compared using the unpaired t test. The probabilities of PFS and OS were estimated using the Kaplan-Meier method with 95% confidence intervals (CIs) and compared using the two-tailed Gehan-Wilcoxon test [17]. Cumulative incidences of relapse, NRM, and GVHD were estimated by competing-risk analysis using Gray's method [18]. Relapse and NRM were competing risks for each other. Relapse, death, and graft failure were competing risks for GVHD. An unadjusted landmark analysis setting day 18 (the median time to engraftment) as the landmark time was used to estimate the cumulative incidence of relapse with respect to GVHD (acute grades II-IV or chronic) as a time-dependent variable, treating NRM as a competing risk for relapse [19]. Data were analyzed with the R program, version 2.12 (R Core Development Team, Vienna, Austria).

RESULTS

Table 1 presents patient characteristics. This was a poor-risk cohort, with 60% receiving at least two prior chemotherapy regimens, 50% having history of chemorefractory disease, and 25% having active disease at alloBMT. Table 2 presents transplantation characteristics. Donors were haplo (n = 22) or HLA-identical (n = 22) first-degree relatives. Grafts in all but one case were marrow derived. Over two thirds of alloBMTs (68%) incorporated high-dose PT/Cy for GVHD prophylaxis, including all RIC alloBMTs (n = 24). The median follow-up for surviving patients was 3.9 years (range, .5 to 13.7 years). At last follow-up, 16 of 44 patients were alive, 15 without relapse. Overall, 32 of 36 assessable patients (92%) engrafted by day 60; of the 4 that did not engraft, 3 had autologous hematopoietic recovery and 1 received a second marrow infusion with subsequent engraftment.

Table 1
Patient Characteristics

Characteristic	Result
Age at alloBMT, yr, median (range)	51 (18-70)
MAC	46 (18-64)
RIC	59 (24-70)
Male sex, n (%)	24 (55)
Histology, n (%)	
Nodal	23 (52)
PTCL, not otherwise specified	7
Angioimmunoblastic T cell lymphoma	6
Anaplastic large cell lymphoma, ALK negative	5
Anaplastic large cell lymphoma, ALK positive	2
Anaplastic large cell lymphoma, ALK unknown	3
Extranodal	14 (32)
Enteropathy-associated T cell lymphoma	6
Hepatosplenic gamma-delta T cell lymphoma	6
Extranodal NK/T cell lymphoma, nasal type	1
Subcutaneous panniculitis-like gamma-delta T-cell	1
Other	7 (16)
Adult T cell leukemia/lymphoma	3
Mycosis fungoides	2
Cutaneous NK cell lymphoma	1
Blastic NK cell lymphoma	1
Remission status at alloBMT, n (%)	
First partial or complete remission, without PIF	14 (32)
Second or greater remission, without PIF	8 (18)
Remission with history of PIF	11 (25)
Active disease at alloBMT	11 (25)
Prior chemotherapy resistance, n (%)	22 (50)
Number of prior therapies, n (%)	
1	18 (40)
2	13 (30)
3 or more	13 (30)
Prior autologous BMT, n (%)	4 (9)
Years from diagnosis to alloBMT, median (range)	.7 (.2-11)
Follow-up of survivors, yr, median (range)	3.9 (.5-13.7)
MAC	4.8 (.8-13.7)
RIC	1.9 (.5-5.1)

PIF indicates primary induction failure; ALK, anaplastic lymphoma kinase.

Donor lymphocyte infusion (DLI) was used sparingly in this cohort and was not given for mixed chimerism alone. Decisions to pursue DLI in the setting of relapse were based on the timing of relapse, GVHD history, and the use of haplo versus HLA-matched grafts. Three patients did receive DLI. In two cases, DLI was pre-emptively given within the 6 months after myeloablative, HLA-matched alloBMT in patients without GVHD and with very high-risk disease (hepatosplenic gamma-delta T cell lymphoma and blastic NK lymphoma). Nonetheless, both patients died of relapsed disease shortly after DLI. In the third case, DLI along with involved field radiation therapy was given to a patient with disease relapse 4 years after RIC/haplo alloBMT, resulting in ongoing disease-free survival at the time of data analysis.

The estimated 2-year PFS for all patients was 40% (95% CI, 26% to 55%) and OS was 43% (95% CI, 28% to 59%) (Figure 1A). On unadjusted analysis, there was a tendency toward superior PFS for alloBMT in first remission versus beyond first remission, with an estimated 2-year PFS of 53% (95% CI, 33% to 77%) versus 29% (95% CI, 9% to 45%), $P = .08$ (Figure 1B). Of the 15 patients who remain alive in sustained remission, 10 received alloBMT in first remission; represented among these 10 are especially poor-risk histologies, including adult T cell leukemia/lymphomas, hepatosplenic gamma-delta T cell lymphoma, and subcutaneous panniculitis-like gamma-delta T cell lymphoma.

To investigate other potential prognostic variables with respect to survival outcomes, Kaplan-Meier curves were constructed to compare outcomes for patients with nodal