Biol Blood Marrow Transplant 22 (2016) 1654–1663

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Impact of Donor and Recipient Cytomegalovirus Serostatus on Outcomes of Antithymocyte Globulin–Conditioned Hematopoietic Cell Transplantation

Amit Kalra [1,*], Tyler Williamson [1], Andrew Daly [1,2], M. Lynn Savoie [1,2], Douglas A. Stewart [1,2], Faisal Khan [1,2], Jan Storek [1,2]

[1] *Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada*
[2] *Alberta Bone Marrow and Blood Cell Transplant Program, Alberta Health Services, Edmonton, Alberta, Canada*

Article history:
Received 17 March 2016
Accepted 19 May 2016

Key Words:
Cytomegalovirus
Antithymocyte globulin

A B S T R A C T

Although previous studies involving allogeneic hematopoietic cell transplantation (HCT) without in vivo T cell depletion by rabbit antithymocyte globulin (ATG) have reported a substantial survival difference between D−R− and D+R− patients, but little to no survival difference between D−R+ and D+R+ patients (D, donor; R, recipient; +, cytomegalovirus [CMV] seropositive; −, CMV seronegative), whether this applies to HCT using ATG is unknown. We studied 928 patients who underwent myeloablative HCT for hematologic malignancies in Alberta between 1999 and 2014 who received graft-versus-host disease (GVHD) prophylaxis using ATG (Thymoglobulin, 4.5 mg/kg) in addition to methotrexate and cyclosporine. D−R− and D+R− patients had similar survival (no significant difference). D−R+ patients had a substantially lower survival than D+R+ patients (41% versus 59% at 5 years; $P = .001$). This difference was attributed to higher nonrelapse mortality, apparently due to higher GVHD-associated mortality. Survival rates were also lower for D−R+ HLA-matched sibling transplant recipients compared with D+R+ HLA-matched unrelated donor transplant recipients (44% versus 66% at 5 years; $P = .009$). In conclusion, when using ATG, choosing a seronegative donor for a seronegative patient is relatively unimportant, whereas choosing a seropositive donor for a seropositive patient is important, even if this requires the use of a seropositive matched unrelated donor graft.

INTRODUCTION

Cytomegalovirus (CMV) infection and CMV disease are major causes of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HCT) [1]. Although CMV antigenemia and DNAemia-guided preemptive therapy have markedly reduced the incidence of CMV disease [2-6], CMV continues to contribute to adverse HCT outcomes [7,8], via poorly defined mechanisms [9,10].

Selecting a CMV-seronegative donor for a CMV-seronegative recipient is a commonly accepted practice based on multiple reports of worse survival of seronegative recipients receiving grafts from seropositive donors compared with grafts from seronegative donors [1,9,11-13]. For seropositive recipients, there has been a weak preference for a seropositive donor, with studies showing either equal or marginally improved survival with a seropositive donor [9,12,13]. However, this practice is based on studies in which graft-versus-host disease (GVHD) prophylaxis for most or all patients did not include a polyclonal rabbit antithymocyte globulin (ATG; ie, Thymoglobulin or ATG-F). We have found that with ATG, survival is markedly inferior in seropositive recipients of grafts from seronegative donors (D−R+) compared with seropositive recipients of grafts from seropositive donors (D+R+) [14]. ATG use is likely to increase, given the 5 randomized studies showing a decreased incidence of chronic GVHD without impacting survival [15-19]. Thus, we considered it important to extend our previous study [14] to include more patients and longer follow-up. Moreover, we wished to address the following additional questions: (1) For seronegative recipients, when ATG is used, is it true that outcomes are worse if the donor is seropositive rather than seronegative, and (2) given the markedly worse outcomes of D−R+ transplants compared with D+R+ transplants when using ATG, are the outcomes of D−R+

Financial disclosure: See Acknowledgments on page 1662.
* Correspondence and reprint requests: Amit Kalra, MBBS, MS, 3330 Hospital Dr NW, Calgary, AB T2N 4N1, Canada.
E-mail address: akalra@ucalgary.ca (A. Kalra).

http://dx.doi.org/10.1016/j.bbmt.2016.05.020
1083-8791/

transplants from HLA-matched siblings worse than those of D+R+ transplants from unrelated donors? Answers to these questions should influence donor selection for patients whose GVHD prophylaxis includes ATG. Our center is in a unique position to answer these questions because we have routinely used ATG since 1999, along with relatively uniform conditioning with chemotherapy/radiotherapy and supportive care.

PATIENTS AND METHODS

Patients

Charts of 955 adult patients who underwent first allogeneic bone marrow or peripheral blood stem cell HCT for a hematologic malignancy in Calgary between 1999 and 2014 were reviewed. Among these patients, 298 had been studied for clinical outcomes in a previous study by our group [14]. A waiver of consent was obtained from our Research Ethics Board. Patients were excluded from the analysis if they fulfilled 1 of the following criteria: (1) graft manipulation other than red blood cell or plasma depletion (n = 1), (2) unknown or indeterminate CMV serostatus of the donor or recipient (n = 18), (3) incomplete HLA typing (HLA-A, -B, and -DRB1 typing required for siblings, and −A, −B, −C, and -DRB1 typing required for nonsiblings [−A, −B, and −C typing was serologic until 2003 and DNA-based thereafter; -DRB1 typing was always DNA-based]) (n = 3), and (4) GVHD prophylaxis not including ATG (n = 5). After excluding these 27 patients, a total of 928 patients were analyzed. Clinical and demographic characteristics of these 928 patients are presented in Tables 1 and 2.

Transplantation

Conditioning regimens typically consisted of fludarabine (50 mg/m^2/day i.v. on days −6 to −2) and busulfan (~3.2 mg/kg/day i.v. on days −5 to −2 in most patients, adjusted according to pharmacokinetics), with or without total body irradiation (TBI; 4 Gy in 2 fractions on days −1 and 0). ATG (Thymoglobulin; Sanofi/Genzyme, Cambridge, MA) was given to all patients (0.5 mg/kg i.v. on day −2, 2.0 mg/kg on day −1, and 2.0 mg/kg on day 0) [20,21]. GVHD prophylaxis also included methotrexate (15 mg/m^2 on day +1 and 10 mg/m^2 on days +3, +6, and +11) plus cyclosporine from day −1 up to 3-6 months post-transplantation (targeting trough plasma levels of 200-400 ng/mL) or longer in the event of GVHD.

Supportive care was similar for all patients. No antibacterial prophylaxis was given routinely (except for trimethoprim-sulfamethoxazole for *Pneumocystis* prophylaxis). *Pneumocystis* prophylaxis was given until 6 months post-transplantation or longer (in cases of GVHD requiring systemic therapy). Antifungal prophylaxis was usually with fluconazole from day 0 to day +28. Acyclovir or valacyclovir was used until 6-24 months post-transplantation or longer (in cases of GVHD requiring systemic therapy). All blood products were irradiated and CMV-safe (either seronegative or leukoreduced). CMV antigenemia or DNAemia was monitored, and preemptive therapy was used as described below. No Epstein-Barr virus (EBV) DNAemia monitoring was done in 1999-2010. In 2011-2014, EBV DNAemia was monitored weekly, and post-transplantation lymphoproliferative disorder was treated promptly with rituximab [22].

Acute GVHD (aGVHD) was graded according to Glucksberg/Seattle consensus criteria [23]. Grade II-IV aGVHD was treated with systemic corticosteroids with or without other immunosuppressive modalities. Chronic GVHD (cGVHD) in this retrospective chart review was diagnosed based on clinical manifestations irrespective of the time of onset based on the National Institutes of Health (NIH) consensus criteria [24]. However, due to insufficient information in many charts regarding cGVHD score, cGVHD was scored as not needing systemic therapy (NNST) and needing systemic therapy (NST). Systemic therapy (corticosteroids with or without other immunosuppressive modalities) was used per our standard practice for extensive cGVHD per the Seattle criteria [25] or moderate-severe cGVHD per the NIH criteria [24]. Significant GVHD was defined as aGVHD grade II-IV or cGVHD requiring systemic immunosuppressive therapy.

CMV Monitoring and Preemptive Therapy

Surveillance for CMV reactivation was performed weekly from engraftment until typically day +100 post-transplantation by CMV pp65 antigenemia [26] (1999-2007) or CMV DNAemia (2008-2014). The DNAemia was measured using an in-house quantitative polymerase chain reaction

Table 1
Patient Characteristics

Characteristic	Total Cohort			CMV-Seronegative Patients			CMV-Seropositive Patients		
	R− (n = 397)	R+ (n = 531)	*P* Value	D−R− (n = 277)	D+R− (n = 120)	*P* Value	D+R+ (n = 331)	D−R+ (n = 200)	*P* Value
Recipient age, yr, median (range)	46 (16-66)	49 (18-66)	.008	45 (16-66)	47.5 (19-66)	.016	50 (18-66)	47 (18-66)	.12
Donor age, yr, median (range)	37 (14-69)	39 (10-73)	.26	34 (14-69)	44.5 (19-67)	.001	41 (15-73)	37 (10-67)	.004
Donor/recipient sex, n (%)			.41			.058			.92
Male/male	154 (39)	191 (36)		116 (42)	38 (32)		120 (36)	71 (35.5)	
Male/female	82 (21)	139 (26)		64 (23)	18 (15)		76 (23)	63 (31.5)	
Female/male	101 (25)	102 (19)		63 (23)	38 (32)		69 (21)	33 (16.5)	
Female/female	60 (15)	99 (19)		34 (12)	26 (22)		66 (20)	33 (16.5)	
Disease stage, n (%)*			.16			.275			.85
Good risk	201 (51)	294 (55)		135 (49)	66 (55)		182 (55)	112 (56)	
Poor risk	196 (49)	237 (45)		142 (51)	54 (45)		149 (45)	88 (44)	
Graft type, n (%)			.02			.34			.43
Bone marrow	56 (14)	48 (9)		36 (13)	20 (17)		27 (8)	21 (10.5)	
Peripheral blood stem cells	341 (86)	483 (91)		241 (87)	103 (83)		304 (92)	179 (89.5)	
Conditioning, n (%)			.43			.21			.33
Flu + Bu + ATG + TBI	225 (57)	322 (61)		163 (59)	62 (52)		197 (60)	125 (62.5)	
Flu + Bu + ATG	164 (41)	201 (38)		107 (39)	57 (47)		127 (38)	74 (37)	
Other chemotherapy/TBI† + ATG	8 (2)	8 (1)		7 (2)	1 (1)		7 (2)	1 (0.5)	
Donor type, n (%)			.46			.001			.001
HLA-matched sibling	182 (46)	267 (50)		112 (40)	70 (58)		185 (56)	82 (41)	
8/8 unrelated	147 (37)	192 (36)		117 (42)	30 (25)		104 (31)	88 (44)	
7/8 unrelated	50 (13)	53 (10)		32 (12)	18 (15)		33 (10)	20 (10)	
6/8 unrelated	3 (0.7)	4 (0.7)		3 (1)	0 (0)		1 (0.3)	3 (1.5)	
8/8 related nonsibling	1 (0.2)	2 (0.3)		1 (0.3)	0 (0)		2 (0.6)	0 (0)	
7/8 related nonsibling	8 (2)	6 (1)		7 (2)	1 (0.8)		1 (0.3)	5 (2.5)	
6/8 related nonsibling	4 (1)	7 (1)		3 (1)	1 (0.8)		5 (1.5)	2 (1)	
5/8 related nonsibling	2 (0.5)	0 (0)		2 (0.7)	0 (0)		0 (0)	0 (0)	

Flu, fludarabine; Bu, busulfan.
Percentages are rounded to zero decimal point, except if ≤1%, in which case the percentages are rounded to 1 decimal point.
* Good risk disease was defined as primary acute leukemia (acute myelogenous leukemia, acute lymphocytic leukemia, biphenotypic) in first remission, chronic myeloid leukemia in first chronic or accelerated phase, myelodysplasia with <5% marrow blasts or aplastic anemia. All other diseases/disease stages were considered poor risk (including all patients with myelofibrosis, chronic myelomonocytic leukemia lymphoma, multiple myeloma).
† Other chemotherapy/TBI included combinations of VP16 (etoposide), melphalan, cytarabine, fludarabine, busulfan, and TBI.