Biol Blood Marrow Transplant 19 (2013) 1731–1739

Impact of Graft-versus-Host Disease on Allogeneic Hematopoietic Cell Transplantation for Adult T Cell Leukemia-Lymphoma Focusing on Preconditioning Regimens: Nationwide Retrospective Study

Takashi Ishida [1,*], Masakatsu Hishizawa [2], Koji Kato [3], Ryuji Tanosaki [4], Takahiro Fukuda [5], Yoshifusa Takatsuka [6], Tetsuya Eto [7], Yasushi Miyazaki [8], Michihiro Hidaka [9], Naokuni Uike [10], Toshihiro Miyamoto [3], Mitsuru Tsudo [11], Hisashi Sakamaki [12], Yasuo Morishima [13], Ritsuro Suzuki [14], Atae Utsunomiya [6]

[1] *Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan*
[2] *Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan*
[3] *Department of Medicine and Biosystemic Science, Kyushu University, Fukuoka, Japan*
[4] *Department of Blood Transfusion and Cellular Therapy, National Cancer Center Hospital, Tokyo, Japan*
[5] *Division of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan*
[6] *Department of Hematology, Imamura Bun-in Hospital, Kagoshima, Japan*
[7] *Department of Hematology, Hamanomachi Hospital, Fukuoka, Japan*
[8] *Department of Hematology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan*
[9] *Department of Hematology, National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan*
[10] *Department of Hematology, National Kyushu Cancer Center, Fukuoka, Japan*
[11] *Department of Hematology, Osaka Red Cross Hospital, Osaka, Japan*
[12] *Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, Tokyo, Japan*
[13] *Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan*
[14] *Department of Hematopoietic Stem Cell Transplantation Data Management/Biostatistics, Nagoya University, Nagoya, Japan*

Article history:
Received 8 August 2013
Accepted 23 September 2013

Key Words:
HTLV-1
ATL-related mortality
TRM
Mogamulizumab

A B S T R A C T

Allogeneic hematopoietic cell transplantation (HCT), but not autologous HCT, can provide long-term remission in some patients with adult T cell leukemia-lymphoma (ATL). We retrospectively analyzed the effects of acute graft-versus-host disease (GVHD) among the 616 patients with ATL who survived at least 30 days after allogeneic HCT with other than cord blood grafts. Multivariate analyses treating the occurrence of GVHD as a time-varying covariate demonstrated an association between grade I-II acute GVHD and favorable overall survival (OS) (hazard ratio [HR], 0.634; 95% confidence interval [CI], 0.477 to 0.843), whereas grade III-IV acute GVHD showed a trend toward unfavorable OS (HR, 1.380; 95% CI, 0.988 to 1.927) compared with nonacute GVHD. In subsequent multivariate analyses of patients who survived at least 100 days after HCT (n = 431), the presence of limited chronic GVHD showed a trend toward favorable OS (HR, 0.597; 95% CI, 0.354 to 1.007), and extensive chronic GVHD had a significant effect on OS (HR, 0.585; 95% CI, 0.389 to 0.880). There were no significant interactions between myeloablative conditioning or reduced-intensity conditioning with OS even when acute GVHD was absent or present at grade I-II or grade III-IV or when chronic GVHD was absent, limited, or extensive. This study demonstrates the actual existence of graft-versus-ATL effects in patients with ATL regardless of whether myeloablative conditioning or reduced-intensity conditioning is used.

INTRODUCTION

Adult T cell leukemia-lymphoma (ATL) is an aggressive peripheral T cell neoplasm caused by human T cell lymphotropic/leukemia virus type 1 (HTLV-1). It has a very poor prognosis, and it has been generally accepted that conventional chemotherapeutic agents alone, even including zidovudine/IFN-α, yield few or no long-term remissions or potential cures in patients with ATL [1-6]. Although early experience in myeloablative chemoradiotherapy together with autologous hematopoietic cell rescue for ATL has been associated with high incidences of relapse and fatal toxicities [7], allogeneic hematopoietic cell transplantation (HCT) has been explored as a promising alternative treatment that can provide long-term remission in a proportion of patients with ATL [8-10].

We previously performed a nationwide retrospective study of patients with ATL who underwent allogeneic HCT in Japan, with special emphasis on the effect of the graft source. We concluded that allogeneic HCT using currently available sources is an effective treatment in selected patients with ATL, but that the use of unrelated cord blood as a stem cell source is associated with lower survival [11]. Our results suggest that allogeneic bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT) could be considered the more standard transplantation forms compared with unrelated cord blood transplantation (CBT) for ATL.

Financial disclosure: See Acknowledgments on page 1738.

* Correspondence and reprint requests: Takashi Ishida, MD, PhD, Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-chou, Mizuho-ku, Nagoya, Aichi, 467-8601, Japan.
E-mail address: itakashi@med.nagoya-cu.ac.jp (T. Ishida).

1083-8791/$ – see front matter © 2013 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.09.014

As the next step, we conducted a nationwide retrospective study of patients with ATL who underwent allogeneic HCT other than CBT, with special emphasis on the effects of the preconditioning regimen, whether conventional myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC). No significant difference in overall survival (OS) was observed between patients receiving MAC and those receiving RIC, but a trend toward RIC contributing to better OS in older patients was noted. Thus, we conclude that allogeneic HCT not only with MAC, but also with RIC, is an effective treatment resulting in long-term survival in selected patients with ATL [12].

ATL has a long latency and occurs in older individuals at a median age of nearly 66 years. The median age at diagnosis of ATL has been increasing over the last few decades [13]. Accordingly, the proportion of patients with ATL undergoing HCT with RIC is currently increasing in relation to HCT with MAC. It is thought that compared with HCT with MAC, allogeneic HCT with RIC depends more on donor cellular immune effects after transplantation and less on the cytotoxic effects of the conditioning regimen to eradicate residual tumor cells. In this context, RIC might be suitable for ATL, given that several reports have indicated the high immunogenicity of ATL cells [14-18] and even the existence of graft-versus-HTLV-1 and/or graft-versus-ATL effects [19-21].

Although we previously reported the impact of post-transplantation immune reactions, graft-versus-host disease (GVHD), on outcomes in patients with ATL [21], our cohort included CBT recipients whose OS curve had a quite different trajectory from that of BMT and PBSCT recipients [12]. Thus, in the present study, we evaluated whether acute and chronic GVHD affect outcomes in patients with ATL undergoing allogeneic HCT other than unrelated CBT, with special emphasis on the effects of the preconditioning regimen. Our present analysis included the previous cohort (1996 to 2005) [21] with updated clinical information, as well as data on 1 patient who underwent allogeneic HCT in 1995 and patients who underwent allogeneic HCT between 2006 and 2010.

PATIENTS AND METHODS

Data Collection

Data on patients with ATL who had undergone a first allogeneic BMT, PBSCT, or BMT + PBSCT were collected from nationwide survey data of the Japan Society for Hematopoietic Cell Transplantation (JSHCT). Cases with missing preconditioning information, acute GVHD, or survival data were excluded, leaving 679 patients. Because the association between the occurrence of acute GVHD and disease-associated mortality was difficult to evaluate in the event of early toxic death, patients who died within 30 days or were censored within 29 days of transplantation (n = 63) were excluded; thus, 616 patients who underwent HCT between March 1995 and December 2010 were included in our analysis.

Data collected for analysis included clinical characteristics, such as age at HCT, sex, disease status at HCT, date of HCT, time from diagnosis of ATL to HCT, performance status (PS) according to the Eastern Cooperative Oncology Group criteria at transplantation, stem cell source, donor–recipient relationship, ATL clinical subtype [22], preconditioning regimen, type of GVHD prophylaxis, date alive at last follow-up, date and cause of death, date of occurrence of acute GVHD and maximum grade of acute GVHD, and grade and date of occurrence of chronic GVHD. The study was approved by the Data Management Committees of the JSHCT, as well as by the Institutional Ethics Committee of Nagoya City University Graduate School of Medical Sciences.

Definitions

OS was defined as the time from HCT until death, and patients who remained alive at the time of the last follow-up were censored. Reported causes of death were reviewed and categorized into ATL-related mortality or treatment-related mortality (TRM). ATL-related mortality was defined as death caused by relapse or progression of ATL based on the judgment of each institution. TRM was defined as any death other than ATL-related mortality.

Table 1
Patient and Transplantation Characteristics by Type of Conditioning Regimen

Characteristic	MAC	RIC	*P* Value
Total patients, n (%)	284 (46.1)	332 (53.9)	
Age at HCT, y, n (%)			
<50	178 (62.7)	43 (13.0)	<.0001
51-55	79 (27.8)	91 (27.4)	
56-60	20 (7.0)	125 (37.7)	
61+	7 (2.5)	73 (22.0)	
Sex, n (%)			
Male	159 (56.0)	160 (48.2)	.0628
Female	125 (44.0)	172 (51.8)	
Disease status at HCT, n (%)			
CR	104 (36.6)	128 (38.6)	.1013
Not in CR	161 (56.7)	194 (58.4)	
Unknown	19 (6.7)	10 (3.0)	
GVHD prophylaxis, n (%)			
CyA + MTX	129 (45.4)	112 (33.7)	<.0001
FK506 + MTX	142 (50.0)	147 (44.3)	
CyA	6 (2.1)	58 (17.5)	
FK506	5 (1.8)	13 (3.9)	
Unknown	2 (0.7)	2 (0.6)	
Stem cell source, n (%)			
BM	216 (76.1)	213 (64.2)	.0015
PBSCs	68 (23.9)	117 (35.2)	
BM + PBSCs	0 (0.0)	2 (0.6)	
Donor–recipient relationship, n (%)			
HLA-matched related	98 (34.5)	120 (36.1)	.3649
HLA-mismatched related	24 (8.5)	40 (12.0)	
Unrelated	160 (56.3)	171 (51.5)	
Unknown	2 (0.7)	1 (0.3)	
PS at HCT, n (%)			
0	111 (39.1)	144 (43.4)	.0012
1	127 (44.7)	154 (46.4)	
2	26 (9.2)	27 (8.1)	
3	3 (1.1)	5 (1.5)	
4	1 (0.4)	1 (0.3)	
Unknown	16 (5.6)	1 (0.3)	
ATL clinical subtype, n (%)			
Chronic/smoldering	11 (3.9)	10 (3.0)	.5278
Acute	171 (60.2)	189 (56.9)	
Lymphoma	80 (28.2)	97 (29.2)	
Unknown	22 (7.7)	36 (10.8)	
Time from diagnosis to HCT, d, n (%)			
16-153	82 (28.9)	72 (21.7)	.0632
154-204	64 (22.5)	88 (26.5)	
205-307	75 (26.4)	78 (23.5)	
308-4355	63 (22.2)	91 (27.4)	
Unknown	0 (0.0)	3 (0.9)	
Time of HCT, n (%)			
March 1995 to March 2005	75 (26.4)	79 (23.8)	.3119
April 2005 to May 2007	75 (26.4)	79 (23.8)	
June 2007 to February 2009	73 (25.7)	81 (24.4)	
March 2009 to December 2010	61 (21.5)	93 (28.0)	
Grade of acute GVHD, n (%)			
No acute GVHD	80 (28.2)	128 (38.6)	.0111
Grade I-II	148 (52.1)	159 (47.9)	
Grade III-IV	56 (19.7)	45 (13.6)	

Acute GVHD was diagnosed and graded using traditional criteria [23] by the physicians who performed HCT at each institution, as was chronic GVHD [24]. Among the 487 patients who survived at least 100 days after HCT, 431 patients with complete information on the grade and the day of occurrence of chronic GVHD were included in the analysis for chronic GVHD.

Patients undergoing allogeneic BMT or PBSCT were divided into 2 groups, MAC and RIC, based on the preconditioning regimen. MAC and RIC were defined according to Giralt et al. [25] and Bacigalupo et al. [26] with slight modifications. In the present study, MAC was defined as any regimen that includes (1) ≥5 Gy of total body irradiation (TBI) as a single fraction or ≥8 Gy fractionated, (2) busulfan >8 mg/kg orally or the i.v. equivalent, or (3) melphalan >140 mg/m^2. All other regimens were classified as RIC.

Statistical Analysis

Comparisons among the groups were performed using Fisher's exact test as appropriate for categorical variables. The probability of survival was