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Haploidentical stem cell transplantation: anti-thymocyte globulin-based experience

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ABSTRACT

Haploidentical stem cell transplantation (haplo-SCT) with an anti-thymocyte globulin (ATG) preparative regimen is associated with induced immune tolerance, rapid hematopoietic recovery, effective prevention of graft-versus-host disease (GVHD), and lower non-relapse mortality (NRM). This has become a common and successfully applied protocol in patients with hematological diseases undergoing haplo-SCT. Survival rates among patients who undergo unmanipulated haploidentical blood and marrow transplantation (HBMT) with anti-thymocyte globulin (ATG)-based regimens are comparable to those following human leukocyte antigen (HLA)-matched sibling transplantation or unrelated donor transplantation. Unmanipulated HBMT can also be successfully used as a post-remission treatment algorithm for acute lymphoblastic leukemia (ALL) and adult acute myeloid leukemia (AML) in cases with unfavorable cytogenetics. Future investigations should focus on further improving donor selection, optimizing allografts, dealing with primary graft failure, and relapse prophylaxis and treatment.

1. Introduction

Successful establishment of multiple haploidentical stem cell transplantation (haplo-SCT) protocols with promising outcomes—including T-cell–replete (TCR) and T-cell–depleted (TCD) transplants—provides alternative treatment options for patients lacking human-leukocyte antigen (HLA)-matched related or unrelated donors [1–23] Stem cells from haploidentical donors have the advantages of widespread availability and ease of procurement, and the shift from TCD grafts to unmanipulated marrow and/or peripheral blood stem cells has made haplo-SCT easier to perform [2,7,24,25].

We previously established a protocol for unmanipulated haploidentical blood and marrow transplantation (HBMT) based on immune tolerance induction using granulocyte colony-stimulating factor (G-CSF) and anti-thymocyte globulin (ATG) [26,27], which shows promising results [2,7,28,29]. Over the last decade, a series of studies from Peking University demonstrated that unmanipulated HBMT can lead to rapid immune recovery [30,31], desirable health-related quality of life [32], and a survival rate comparable to that following HLA-matched sibling transplantation (MSDT) or unrelated donor transplantation (MUDT) [1,16,17,30]. Furthermore, the HBMT protocol is superior to umbilical cord blood transplantation for treating pediatric hematological malignancies [33]. HBMT can also be successfully used as a post-remission treatment algorithm for acute lymphoblastic leukemia (ALL) and adult acute myeloid leukemia (AML) in cases with unfavorable cytogenetics [5–7].

Several ATG preparative-based haplo-SCT modalities have recently been established, and have become widely used in China and applied in a number of centers in Asia and Europe (Table 1) [4,13,15–21,24,25,34–40]. The present review focuses on recent advances in haplo-SCT with ATG. The improvements are mainly discussed with regards to conditioning regimens, allograft choice, and prophylaxis of graft-versus-host disease (GVHD). We also review the results of prospective comparisons of ATG-based haplo-SCT protocols with MSDT and MUDT. Finally, we discuss future directions, which should focus on selecting the best donor, optimizing allografts, dealing with primary graft failure, and relapse prophylaxis and treatment.

2. Transplant outcomes after haplo-SCT with ATG-based regimens

The clinical outcomes of haplo-SCT with ATG-based regimens have been previously reviewed by our group and others [8,9,41]. Table 1 summarizes the recent reported clinical outcomes of this

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Table 1
Recent* informative trials and results of haploidentical stem cell transplantation with ATG preparative regimen.

Reference	Pts (no.)	Diagnosis	Graft	ANC	PLT	GVHD		TRM	Relpase	LFS	OS
						Acute II-IV	cGVHD				
Wang Y, et al, 2014 [2]	1,210	HM	G-BM+G-PB	13 (8-49)	16 (5-100)	40%	50%	17% at 3 yr	17% at 3 yr	67% at 3 yr	70% at 3 yr
Chen H, et al, 2015 [29]	101	Ph^+ ALL	G-BM+G-PB	12 (7-27)	14 (9-150)	38%	68.5% at 5 yr	15.6% at 5 yr	18% at 5 yr	65.8% at 5 yr	74% at 5 yr
Mo XD, et al, 2014 [42]	81	Ph^- ALL LR	G-BM+G-PB	12 (9-24)	15 (8-250)	42%	65.5% at 3 yr	16.2% at 3 yr	17.8% at 3 yr	68.2% at 3 yr	72.2% at 3 yr
	102	Ph^- ALL HR	G-BM+G-PB	13 (10-23)	16 (7-161)	36.3%	59.4% at 3 yr	18% at 3 yr	15.4% at 3 yr	67.6% at 3 yr	74.9% at 3yr
Lin X, et al, 2015 [38]	105	HM	G-PB	14 (10-25)	16 (9-38)	21.9%	24.1% at 2 yr	30.5% at 3 yr	21.9% at 3 yr	41.1% at 3 yr	50.6% at 3yr
Shin SH, et al, 2015 [21]	60	MDS	G-PB	12 (8-23)	15 (6-132)	36.7%	48.3%	23.3% at 2yr	34.8% at 2 yr	41.9% at 2 yr	46.6% at 2 yr
Peccatori J, et al, 2015 [24]	121	HM	G-PB	17 (11-61)	19 (7-154)	35%	47% at 2 yr	31% at 3 yr	48% at 3 yr	20% at 3 yr	25% at 3 yr
Luo Y, et al, 2014 [4]	99	HM	G-PB	12 (8-24)	15 (6-53)	42.4%	41.4% at 2 yr	30.5% at 5yr	14.2% at 5yr	58.3% at 5yr	60.8% at 5yr
Chen J, et al, 2014 [23]	50	HM	G-PB+UCB	13 (11-20)	15 (11-180)	20%	19.3% at 1 yr	16.2% at 1 yr	19.8% at 1 yr	64% at 1 yr	78.6% at 1 yr
Tang BL, et al, 2015 [39]	17	HM	G-PB	12 (11-15)	17 (11-117)	35.3%	29.4%	29.4% at 180d	NA	67.4% at 1yr	67.4% at 1yr
Yahng SA, et al, 2015 [40]	80	AML	G-PB	11	10	47.5%	45%	12.2% at 2 yr	26.6% at 2 yr	61.1% at 2 yr	66% at 2 yr
Di Bartolomeo P, et al, 2013 [45]	80	HM	G-BM	21 (12-38)	28 (14-185)	24%	17% at 2 yr	36% at 3 yr	21% at 1 yr	38% at 3 yr	45% at 3yr
Xu LP, et al, 2012 [19]	19	SAA	G-BM+G-PB	12 (10-29)	18 (8-180)	42.1%	56.2%	35.4% at 2 yr	NA	NA	64.5 at 2 yr
Gao L, et al, 2014 [43]	26	SAA	G-PB+G-BM	13 (11-19)	13 (10-21)	8.0%	40%	15.4% at 2 yr	NA	NA	84.6% at 2 yr

ATG = antithymocyte globulin; Pts = patients; No. = number; ANC = absolute neutrophil count; PLT = platelet; GVHD = graft-versus-host disease; cGVHD = chronic GVHD; TRM = transplant-related mortality; LFS = leukemia free survival; OS = overall survival; HM = hematological malignancies; G-BM = granulocyte colony-stimulating factor (G-CSF)-primed bone marrow; G-PB = G-CSF-mobilized peripheral blood stem cell grafts; MA = myeloablative; yr = year; AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia; NA = not available.

* Published between 2013 and 2015.

haploidentical protocol [4,16–20,23,24]. The Peking University Group reported data following unmanipulated HBMT in 1,210 subjects over the last 10 years, including the 3-year cumulative incidences of transplant-related mortality (TRM; 17%), relapse (17%), disease-free survival (DFS; 67%), and overall survival (OS; 70%) [2]. More recently, we analyzed clinical data from 101 Philadelphia chromosome–positive (Ph^+) ALL patients who received allo-HSCT at our center. At a median follow-up of 36 months, the 5-year cumulative incidences of relapse and TRM were 20.3% and 15.6%, respectively, while the 5-year probabilities of DFS and OS were 65.8% and 74.0%, respectively [29]. Furthermore, among adults with Ph^- ALL in first complete remission (CR1), the 3-year incidence of relapse mortality was 7.1% in the high-risk (HR) group and 11.1% for the low-risk (LR) group ($P = .498$) and 3-year incidence of TRM was 18.0% in the HR group versus 16.2% in the LR group ($P = .717$). The 3-year probabilities of DFS and OS for the HR versus LR groups were 67.6% versus 68.2% ($P = .896$) and 74.9% versus 72.7% ($P = .981$), respectively [42]. These data suggest that unmanipulated HBMT is a potentially valuable alternative form of transplantation, particularly at experienced centers and in cases with no HLA-identical sibling donor.

Another group from China reported promising outcomes following treatment of hematological malignancies using haplo-SCT with an ATG-based regimen and G-CSF–mobilized peripheral blood (G-PB) as allografts. After a median follow-up of 35 months, the 3-year cumulative incidences of relapse and non-relapse mortality (NRM) were 21.9% and 30.5%, respectively. The 3-year probability of OS was 63.2% for the intermediate-risk group and 39.8% for the HR group, while the 3-year probability of DFS was 61.2% for the intermediate-risk group and 32.2% for the HR group [38]. A group from Korea investigated 60 consecutive patients with myelodysplastic syndrome (MDS) or secondary AML. After a median follow-up of 4 years, they reported a 34.8% incidence of relapse, a 23.3% incidence of NRM, a 46.8% OS rate, and a 41.9% DFS rate [21]. Peccatori et al [24] conducted a prospective phase II multicenter trial analyzing 121 patients, mostly with advanced hematological malignancies, who underwent a myeloablative conditioning regimen with ATG-based prophylaxis of GVHD. They found a 35% incidence of acute GVHD, which was negatively associated with regulatory T cells, and a 47% incidence of chronic GVHD. At 3 years after HSCT, TRM was 31%, relapse incidence was 48%, and the OS rate was 25%. The feasibility and promising outcomes of haplo-SCT with ATG in treating hematological malignancies have been confirmed by researchers from different transplant centers (Table 1) [3–5,21,23,39,40,43–46], suggesting that this transplant modality presents an attractive alternative treatment option for hematological malignancy patients.

In the Peking University, to treat patients with severe aplastic anemia (SAA), a myeloablative regimen was developed, which includes busulfan (Bu) 3.2 mg/kg on days −7 and −6, cyclophosphamide (Cy) 50 mg/kg/d from day −5 to day −2, and rabbit ATG 2.5 mg/kg/d or porcine ATG 20 mg/kg/d also from day −5 to day −2 [19]. All patients who underwent this regimen achieved hematopoietic recovery, with a median of 12 days (range, 10–29 days) to myeloid engraftment, and a median of 18 days (range, 8–180 days) to platelet engraftment. The cumulative incidences of grade II–IV acute GVHD and chronic GVHD were 42.1 ± 11.3% and 56.2 ± 12.4%, respectively. OS was 64.6 ± 12.4%, with a median follow-up of 746 days (range, 90–1970 days) for surviving patients [19]. At another center in China, Gao et al [43] treated 26 patients with SAA using a fludarabine (Flu)/Cy/ATG-based conditioning regimen. They reported a 92.3% engraftment rate, with a median of 13 days (range, 11–19 days) to neutrophil engraftment and 13 days (range, 10–21 days) to platelet engraftment. Of 25 patients, three (12%) developed acute GVHD and 10 (40%) developed chronic GVHD (nine limited and one extensive). The OS rate was