Bone Marrow Transplantation (2021) 56:741–744
https://doi.org/10.1038/s41409-020-01079-8

CORRESPONDENCE

Comparison of myeloablative and reduced intensity conditioning regimens in haploidentical peripheral blood stem cell transplantation

Dipenkumar Modi[1] · Seongho Kim[1,2] · Abhinav Deol[1] · Lois Ayash[1] · Voravit Ratanatharathorn[1] · Joseph P. Uberti[1]

Received: 23 May 2020 / Revised: 24 September 2020 / Accepted: 28 September 2020 / Published online: 16 October 2020

Abstract

Limited information is available on the impact of intensity of conditioning regimens in haploidentical peripheral blood stem cell transplant (haploPBSCT) with post-transplant cyclophosphamide (PTcy). We retrospectively compared outcomes of haplo-PBSCT between myeloablative (MAC) ($n = 24$) and reduced intensity conditioning (RIC) regimens ($n = 65$). Propensity score-based multivariable analyses were performed to adjust confounding effects of baseline characteristics between both groups. Eighty-nine patients underwent haplo-PBSCT between January 2012 and June 2019. For MAC and RIC, the cumulative incidences of grade III–IV acute GVHD were 4.2% and 3.1%, respectively ($p = 0.92$), and chronic GVHD were 18.9% and 36.5%, respectively ($p = 0.08$). Median follow-up for overall survival (OS) after MAC and RIC was 1.86 and 2.2 years, respectively. For MAC and RIC, one-year OS was 68.8% and 67.4%, respectively ($p = 0.85$); one-year relapse rate was 22.4% and 18.3%, respectively ($p = 0.74$); one-year relapse-free survival (RFS) was 56% and 59.7%, respectively ($p = 0.87$); and one-year non-relapse mortality (NRM) was 22% and 21.9%, respectively ($p = 0.58$). Using propensity score-based multivariable analyses, no difference in OS (HR 0.72, $p = 0.51$), relapse (SHR 0.63, $p = 0.42$), RFS (HR 0.74, $p = 0.49$) and NRM (SHR 1.11, $p = 0.87$) was noted between RIC and MAC. Our study shows no difference in outcomes between MAC and RIC regimens in haplo-PBSCT.

T-cell replete haploidentical donor transplant (HIDT) with post-transplant cyclophosphamide (PTcy) has allowed patients lacking matched related or unrelated donor to proceed to transplant. PTcy selectively depletes alloreactive T cells and spares regulatory T lymphocyte, and allows engraftment of stem cells despite HLA disparity [1]. The John Hopkins study reported reduced rates of acute and chronic GVHD and non-relapse mortality (NRM) in HIDT. However, the relapse rate was high at 51% [1]. Use of peripheral blood stem cells (PBSC) has shown to reduce relapse rate compared to BM grafts in HIDT [2], but acute [2, 3] and chronic GVHD [2] rates were higher. Myeloablative conditioning (MAC) regimens have been used safely in HIDT [4–6]. The CIBMTR study demonstrated superior disease-free survival (DFS) with MAC among acute leukemia and MDS patients aged 18–54 years compared to reduced intensity conditioning (RIC) [7]. Conversely, the EBMT study did not observe any difference in leukemia-free (LFS) and overall survival (OS) between MAC and RIC [8]. These studies were however limited by heterogeneity in the conditioning regimens [7, 8], graft source [7, 8], and GVHD prophylaxis [8]. Therefore, the impact of intensity of conditioning regimen remains unclear. Selection of conditioning regimen is often influenced by patient- and disease-related factors. Thus, retrospective analyses are limited by a selection bias. Propensity score-based covariate adjustment (PSCA) is a method, which minimizes the effects of variables which are unevenly distributed. Using PSCA, we compared outcomes of MAC with RIC in

Supplementary information The online version of this article (https://doi.org/10.1038/s41409-020-01079-8) contains supplementary material, which is available to authorized users.

✉ Dipenkumar Modi
modid@karmanos.org

[1] Department of Oncology, Barbara Ann Karmanos Cancer Institute/Wayne State University, 4100 John R, HW04H0, Detroit, MI 48201, USA

[2] Biostatistics Core, Department of Oncology, Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI 48201, USA

haploidentical peripheral blood stem cell transplantation (haplo-PBSCT).

We conducted a retrospective study of 89 adult patients who received mobilized PBSC and underwent haplo-PBSCT between January 2012 and June 2019. All received PTcy, tacrolimus and mycophenolate as GVHD prophylaxis. The Wayne State University Institutional Review Board approved this study. This work was carried out in accordance with the code of ethics of the Declaration of Helsinki for experiments involving humans. Patients received MAC regimen of busulfan and fludarabine, and RIC regimen of either busulfan, fludarabine and low-dose total body irradiation (TBI), or fludarabine, melphalan, and low-dose TBI. The objectives were to compare OS, relapse rate, NRM, relapse-free survival (RFS), and GVHD-free relapse-free survival (GRFS) between groups. Multivariable Cox and subdistribution proportional hazard regression analyses were performed for adjusted HR and SHR, respectively, by PSCA [9]. Propensity scores were estimated using logistic regression models with group as response variable and age, diagnosis, prior transplant, disease risk index (DRI), comorbidity index (CI) and donor age as covariates. Age, donor age, and CI were selected because of their uneven distributions between groups ($p < 0.10$) (Table 1). Other covariates were included because of known clinical confounding factors.

Patient characteristics are shown in Table 1. Out of 89 patients, 24 (27%) received MAC and 65 (73%) received RIC. Assignment of the conditioning regimen was per physician discretion. Patients in the MAC were younger (median age 47 vs 62 years, $p = 0.005$), and their donor age was lower compared to RIC (median age 40 vs 58 years, $p = 0.03$). For MAC and RIC, median time to neutrophil engraftment was 16 and 18 days, respectively ($p = 0.03$), while platelet engraftment time was 21 and 24 days, respectively ($p = 0.18$). One patient (4%) in the MAC and four (6%) in the RIC experienced primary graft failure. Seventy-nine percent patients in the MAC and 69% in the RIC developed grade 1–2 CRS per ASTCT criteria [10], while 8% in the MAC and 6% in the RIC experienced grade 3–4 CRS ($p = 0.27$). For MAC and RIC, the cumulative incidence of grade III–IV acute GVHD (aGVHD) was 4.2% (95% CI, 0.3–18.1%) and 3.1% (0.6–9.6%), respectively ($p = 0.92$); and chronic GVHD (cGVHD) was 18.9% (5.4–38.5%) and 36.5% (24–49%), respectively ($p = 0.08$). The non-significant trend for higher cGVHD in RIC compared to MAC could be related to a lack of power.

The median follow-up for OS was 1.75 years for MAC and 2.28 years for RIC. At 1 year, OS was 68.9% for MAC and 67.4% for RIC (HR, 1.08; 95% CI, 0.48–2.41; $p = 0.85$); and relapse rate was 22.4% for MAC and 18.3% for RIC (SHR, 0.84; 0.30–2.33; $p = 0.74$). The multivariable analysis by PSCA to adjust for age, diagnosis, prior transplant, DRI, CI, and donor age revealed an adjusted HR of 0.72 (95% CI, 0.28–1.87; $p = 0.50$) for OS and 0.63 (0.21–1.94; $p = 0.42$) for relapse. At 1 year, RFS was 56.1% for MAC and 59.7% for RIC (HR, 1.06; 95% CI, 0.52–2.17; $p = 0.88$); NRM was 22% for MAC and 21.9% for RIC (SHR, 1.33; 0.49–3.59; $p = 0.58$); and GRFS was 37.4% for MAC and 43% for RIC (HR, 1.02; 0.55–1.88; $p = 0.96$) (Figs. S1–S3). After PSCA, adjusted HR for RFS, NRM and GRFS was 0.74 (95% CI, 0.32–1.73, $p = 0.49$), 1.11 (0.31–3.96; $p = 0.87$) and 0.82 (0.39–1.69; $p = 0.58$). Major causes of death included disease relapse (26%), infection (24%), multiorgan failure (21%), and GVHD (12%).

In this single-center retrospective study comparing long-term outcomes of haplo-PBSCT between MAC and RIC, we did not observe any difference in transplant outcomes. We used propensity score-based multivariable covariate adjustment to nullify the influence of some of the biological factors driving selection of the conditioning regimen. Our results are different than the CIBMTR study which evaluated outcomes of MAC ($n = 526$) and RIC ($n = 799$) in acute leukemia and MDS patients undergoing HIDT [7]. DFS was lower (HR 1.34, $p = 0.007$) and relapse rate was higher (SHR 1.51, $p = 0.001$) with RIC in patients aged 18–54 years compared to MAC. Outcomes were similar in patients aged 55–70 years. The major difference between the CIBMTR study and ours was that approximately half of the patients in the CIBMTR study received PBSC compared to all patients in our study. The EBMT conducted a similar analysis evaluating MAC ($n = 425$) and RIC ($n = 217$) among acute leukemia patients undergoing HIDT and revealed no difference in LFS and OS [8]. Few differences between the EBMT analysis and ours included 25–32% of patients receiving PTcy, nearly half receiving in-vivo T-cell depleting agents, and 52–64% receiving PBSC in the EBMT analysis. Another single-center study comparing outcomes of MAC and RIC haplo-PBSCT reported lower relapse rate and higher NRM with MAC [11]. Approximately 85% of patients received fludarabine-cyclophosphamide-TBI-based NMA regimen in that study, which might have influenced the relapse rate.

Our study cohort consisted of high-risk population as indicated by active disease in more than half of the patients. Our relapse rate was considerably lower than the John Hopkins experience (19% vs 51%) [1]. Use of higher intensity regimens and PBSC allograft might have contributed to this difference. We did not observe any adverse effect of conditioning regimens on neutrophil and platelets engraftment. Recovery of neutrophils and platelets was slower compared to non-PTcy based GVHD prophylaxis, which could be secondary to myelosuppressive effect of PTcy [12].

Limitation of our study includes a possible selection bias because the decision of the conditioning regimen was based on physician discretion and so, the MAC group was small.

Table 1 Baseline patient characteristics.

	Myeloablative conditioning (MAC) ($N = 24$)	Reduced conditioning (RIC) ($N = 65$)	All ($N = 89$)	p
Age at transplant—median (range)	47 (21,78)	62 (22,78)	60 (21,78)	***0.005***
Sex—no. (%)				0.190
Male	18 (75)	37 (57)	55 (62)	
Female	6 (25)	28 (43)	34 (38)	
Race—no. (%)				0.560
Caucasian	13 (54)	43 (66)	56 (63)	
African American	8 (33)	15 (23)	23 (26)	
Others	3 (12)	7 (11)	10 (11)	
Prior transplant—no. (%)				>0.99
Yes	4 (17)	12 (18)	16 (18)	
Type of prior transplant—no. (%)				0.744
Allogeneic	2 (8)	7 (11)	9 (10)	
Autologous	2 (8)	4 (6)	6 (7)	
Umbilical cord blood	0 (0)	1 (2)	1 (1)	
Diagnosis—no. (%)				0.190
Acute Myeloid Leukemia	17 (71)	28 (43)	45 (51)	
Myelodysplastic syndrome	2 (8)	16 (25)	18 (20)	
Non-Hodgkin's Lymphoma	0 (0)	4 (6)	4 (4)	
Chronic Myelomonocytic Leukemia	1 (4)	1 (2)	2 (2)	
Acute Lymphoblastic Leukemia	1 (4)	10 (15)	11 (12)	
Multiple Myeloma	1 (4)	1 (2)	2 (2)	
Myeloproliferative disorders	1 (4)	4 (6)	5 (6)	
Hodgkin's Lymphoma	1 (4)	1 (2)	2 (2)	
Disease status at transplant—no. (%)				0.254
Complete remission	9 (38)	30 (46)	39 (44)	
Not in complete remission	4 (17)	17 (26)	21 (24)	
Relapse and refractory disease	11 (46)	18 (28)	29 (33)	
Disease status at transplant: AML/ALL—no. (%)				0.296
Complete remission 1	6 (35)	5 (18)	11 (24)	
Complete remission 2	3 (18)	11 (39)	14 (31)	
Complete remission 3	0 (0)	1 (4)	1 (2)	
Relapse-Refractory disease	8 (47)	11 (39)	19 (42)	
Disease status at transplant: MDS/CMML—no. (%)				>0.99
Complete remission	0 (0)	2 (12)	2 (10)	
Not in complete remission	3 (100)	15 (88)	18 (90)	
Disease status at transplant: Myeloma/Lymphoma - no. (%)				-
Complete remission	-	1 (25)	1 (25)	
Relapse-Refractory disease	-	3 (75)	3 (75)	
Admit KPS—median (range)[a]	80 (60,90)	80 (70,100)	80 (60,100)	0.646
Comorbidity index—median (range)[b]	0.5 (0,5)	1 (0,4)	1 (0,5)	0.096
Disease risk index—no. (%)				0.122
Low	2 (8)	1 (2)	3 (3)	
Intermediate	8 (33)	32 (49)	40 (45)	
High	13 (54)	24 (37)	37 (42)	
Very high	1 (4)	8 (12)	9 (10)	
CMV serogroup status—no. (%)				0.649
−/−	4 (17)	15 (23)	19 (21)	
−/+	6 (25)	19 (29)	25 (28)	
+/−	2 (8)	8 (12)	10 (11)	
+/+	12 (50)	23 (35)	35 (39)	

Table 1 (continued)

	Myeloablative conditioning (MAC) ($N = 24$)	Reduced conditioning (RIC) ($N = 65$)	All ($N = 89$)	p
ABO match—no. (%)[b]				0.307
Matched	14 (58)	39 (60)	53 (60)	
Major mismatch	4 (17)	17 (26)	21 (24)	
Minor mismatch	6 (25)	8 (12)	14 (16)	
Donor age—median (range)	40.5 (17,78)	58 (19,78)	52 (17,78)	***0.033***
Infused CD34—median (range)[c]	6.74 (2.4,14.17)	8.15 (1.29,23.96)	7.91 (1.29,23.96)	0.312
HLA match—no. (%)				0.331
4/8	19 (79)	42 (65)	61 (69)	
5/8	4 (17)	18 (28)	22 (25)	
6/8	0 (0)	4 (6)	4 (4)	
7/8	1 (4)	1 (2)	2 (2)	

[a]Data are not available for six patients.

[b]Data are not available for one patient.

[c]Data are not available for four patients.

However, uniform conditioning regimens, GVHD prophylaxis, graft source and supportive care could be considered strengths of the study. Since our study is restricted to single center, it limits the heterogeneity associated with multicenter studies. In conclusion, our study shows efficacy of MAC and RIC in haplo-PBSCT recipients. RIC haplo-PBSCT results in equivalent long-term outcomes when compared to MAC regimens.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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