Transfusion and Apheresis Science xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

Age does not matter: Mobilization and harvesting are safe and effective for elderly allogeneic peripheral hematopoietic stem cell donors

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Donor
Age
Allogeneic

ABSTRACT

It took several years to succeed safe hematopoietic stem cell transplantations. HLA-matched unrelated donors have become the most common donor source for allogeneic hematopoietic stem cell transplants worldwide. The sibling donor may have more comorbidity and decreased regenerative potential of stem and immune cells. The purpose of this retrospective study was to examine whether aging had any negative effect on aging donor or patient. 27 patients who received a hematopoietic stem cell transplantation (HSCT) from February 2013 to May 2016 and their donors were analyzed. We showed that transplantation from older relative donor was feasible. Adverse event rate was low. Donors tolerated the procedure very well. Good CD34+ cell harvest was possible.

Contents

1. Introduction

In 1957, Thomas ED published the first Bone Marrow Transplantation (BMT) for acute leukemia patients. None of the patients survived [1]. In 1968, three patients suffering from a congenital immune deficiency were successfully transplanted with hematopoietic HLA-matched sibling donor stem cells [2]. In 1979, Hansen and colleagues performed the first successful unrelated donor marrow transplant for an acute leukemia patient [3]. HLA-matched unrelated donors have become the most common donor source for allogeneic hematopoietic cell transplants [4]. The National Marrow Donor Program (NMDP) was established in 1986 to recruit and conduct HLA typing of unrelated donors. Current NMDP obligation for donor age is 18-60 years. The National Donor Program in Turkey is named as "Türkök" and requires that donors must be between the ages of 18 and 50 years. Turkey is a developing country with limited sources. Recruited unrelated donor count is below NDMP. Unlike United States, patients usually have more than one sibling and the percentage of finding a matched sibling donor is higher. For older-age patients a sibling donor is usually of an age similar to that of the patient. Therefore, the sibling donor may have more comorbidity and decreased regenerative potential of stem and immune cells.

The purpose of this retrospective study was to examine whether aging had any negative effect on aging donor or patient.

2. Patients and methods

27 patients who received hematopoietic stem cell transplantation (HSCT) from February 2013 to May 2016 and their donors were

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https://doi.org/10.1016/j.transci.2017.11.014
1473-0502/

Table 1
Patient and donor characteristics.

Parameters		n	Percent (%)
Relation	Mother	4	14.8
	Brother	22	81.5
	Cousin	1	3.7
Patient sex	Male	17	63.0
	Female	10	37.0
Donor sex	Male	14	51.9
	Female	13	48.1
Comorbidity	BPH	1	3.7
	DM,HT	2	7.4
	DM, HT, OA	1	3.7
	Epilepsy	1	3.7
	Hypothyroidism	1	3.7
	HT	10	37.0
	HT, nephrectomy	1	3.7
	HT, hypothyroidism	1	3.7
	HT, CAD	1	3.7
	Osteoporosis	1	3.7
	None	7	25.9
Type of Disease	ALCL	1	3.7
	AML	14	51.9
	DLBCL	1	3.7
	CML	1	3.7
	LL	1	3.7
	MCL	2	7.4
	MDS-EB	5	18.5
	MM	1	3.7
	Myelofibrosis	1	3.7

BPH: Benign prostate hyperplasia, DM: Diabetes mellitus, HT: Hypertension, OA: Osteoarthritis, CAD: Coronary Artery Disease. ALCL: Anaplastic large cell lymphoma, AML: Acute myeloid leukemia, DLBCL: Diffuse large B cell lymphoma. CML: Chronic myeloid leukemia, LL: Lymphoblastic leukemia, MCL: Mantle cell lymphoma, MDS-EB: Myelodysplastic syndrome with excess blast, MM: Multiple myeloma.

analyzed. Data were retrospectively collected from our transplant data base. Patients and donors were matched for HLA A, B, C, DRB1 and DQB1 by low resolution DNA-typing as appropriate.

2.1. Treatment

Myeloablative conditioning (MA) regimen consisted of intravenous Busulfan 3,2 mg/kg on days (−7 to −4), and Cyclofosfamide 60 mg/kg (−3,−2). Reduced intensity conditioning (RIC) regimen consisted of Busulfan 3,2 mg/kg on days (−6,−5), Cyclofosfamide 350 mg/m^2 (−4 to −2), and Fludarabine 30 mg/m^2 (−4 to −2). Graft versus host disease (GVHD) prophylaxis included intravenous Cyclosporine 1 mg/kg from day −1 and Methotrexate 15 mg/m^2 on day +1 and 10 mg/m^2 on day +3, +6, and +11 in MA regimen. Methotrexate was administered 10 mg/m^2 on day +1, +3, and +6 in RIC regimen. Cyclosporine levels in peripheral blood were monitored in order to adjust treatment. As soon as patients tolerate oral cyclosporine, it was administered.

2.2. Statistical analysis

The statistical analysis was implemented using SPSS version 20.0 (SPSS, Chicago, IL, USA). CD34 count and donor characteristics were compared by Spearman test and Mann-Whitney test. Survival and progression-free survival (PFS) were calculated by using the method of Kaplan and Meier. HLA matching comparisons were calculated by χ^2 test, and Mann-Whitney test. CD34 count and venous access were compared by Mann-Whitney test. GVHD associated deaths were compared with variables by Mann-Whitney test.

3. Results

Patient and donor characteristics are summarized in Table 1. Among the 27 patients included, diagnosis was Acute Myeloid Leukemia (AML) in 14 (51.9%), Myelodysplastic Syndrome Excess Blast (MDS-EB) in 5 (18.5%), Mantle Cell Lymphoma in 2 (7.4%). Donor sex was equally balanced. 14 (51.9%) of them were male and 13 (48.1%) of them were female. Patient sex was in favor of male; 17 (63%) versus 10 (37%). 22 (81.5%) donors were sibling. 4 (14.8%) donors were mothers and 1 (3.7%) donor was cousin. Apheresis count was 1 in 16 (59.3%) in donors and 2 in 11 (40.7%) donors. 11 (40.7%) donors required central venous catheter insertion for stem cell collection. Femoral catheter was inserted to only 1 (3.7%) donor. Subclavian catheter was inserted to 10 (37.0%) donors. No side effect occurred during collection period.

Table 2
Baseline data and apheresis results.

Parameters	Median	Minimum	Maximum
Donor age, years	64	60	76
Donor weight, kg	79	57	100
Peripheral CD34 × 10^6/L	54	12	167
Harvest CD34 × 10^6/L	6.25	4.04	13.61
Patient age, years	64	32	75
neutrophil engraftment	14	11	19
platelet engraftment by day	14	9	25
Hb, g/dL	13.9	11	15.8
Platelet, x10^9/L	234	161	328
White blood cell, x10^9/L	6.72	3.92	11.3
Neutrophil, x10^9/L	3.98	1.41	2.04
Lymphocyte, x10^9/L	2.09	1.1	4.07
Monocyte, x10^9/L	0.5	0.23	5.9

Table 2 summarizes donor age, baseline hematological counts, CD34 counts, and engraftment. Median donor age was 64 (60–76). Median peripheral CD34 count was 54/mL (12–167). Median CD34+ cell harvest count was 6.25 × 10^6/kg. Median patient age was 56 (32–75). The median time to neutrophil and platelet recovery was 14 days for each.

21 (77%) patients died. 11 (52%) of them were transplant related. The leading cause of death were recurrence (23%) and persistent disease (28%). Second cause was acute and chronic GVHD (n = 7, 33%). No significant difference was observed.

Kaplan-Meier analysis showed that estimated PFS was 13.2 months (Fig. 1) and estimated OS was 17.9 months (Fig. 2). No significant survival difference was seen between full match and haploidentical donor transplants. Engraftment days did not differ between them, either. An interesting finding was that peripheral venous stem cell harvest was significantly higher than central venous catheter stem cell harvest (p = 0.013).

4. Discussion

Older donor age has been shown to be associated with poorer outcome of unrelated myeloablative transplants [5]. It has also been described that RIC transplantation was better in patients and younger donors [6]. Since RIC is applied to older patients, their donors are older, too. Advanced donor age means loss of function [7], loss of repopulating ability [8], and impaired homing ability [9]. These may explain the high relapse and therapy related mortality rate in our study. Kollman et al. [5] have presented the largest donor group results. Their data set consisted of 6978 unrelated donor bone marrow transplantations facilitated by the NMDP. Their data suggested that survival rates might be improved if younger donors were selected. They described that younger donors overcome deleterious effects of a partial HLA mismatch. In our study we did not see a survival difference between full match and mismatch donors. Their speculation was to lower the upper threshold of age that NDMP accepts as 60 years. It must be kept in mind that patients' doctors determine the appropriate donor for siblings. This decision may lead to choose a less suitable donor and force a high mortality transplant. When a matched related donor is available, regardless

Please cite this article in press as: Ocakci S, et al. Age does not matter: Mobilization and harvesting are safe and effective for elderly allogeneic peripheral hematopoietic stem cell donors. Transfus Apheresis Sci (2017), https://doi.org/10.1016/j.transci.2017.11.014