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Outcome of Peripheral Blood Allogeneic Hematopoietic Stem Cell Transplantation as a Treatment Option in Patients with Severe Aplastic Anemia Between 40 and 50 years

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BRIEF COMMUNICATION

Outcome of Peripheral Blood Allogeneic Hematopoietic Stem Cell Transplantation as a Treatment Option in Patients With Severe Aplastic Anemia Between 40 and 50 Years

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Abstract

The frontline treatment for patients younger than 40 years with severe aplastic anemia (AA) is allogeneic hematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen-identical sibling donor. However, in patients with severe AA who are older than 40 years, allogeneic HSCT has been found to be associated with increased treatment-related mortality and toxicity, even when matched sibling donors are used. We report our institutional experience with allogeneic HSCT in patients with severe AA between 40 and 50 years. A total of 19 patients with severe AA were included in the study. Overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan–Meier method. The mean age of patients at the time of transplant was 43.79 years, and 57.9% were male. The mortality rate was 36.8%, attributed to infection (10.5%), relapse (15.8%), and renal failure (5.3%) in all cases. Acute graft-versus-host disease (GVHD) occurred in five patients (26.3%), and chronic GVHD occurred in two patients (10.5%). The 5-year OS was 62% and the 5-year DFS was 52%. We found that the patient's age, platelet level prior to transplantation, and the number of CD3 cells infused for each transplant were independent prognostic factors for OS, and the age and sex of the patient, graft rejection, and platelet level prior to transplantation were significant prognostic factors associated with DFS. We recommend that immunosuppressive therapy be considered as a first-line treatment in patients with severe AA who are older than 40 years. Allogeneic HSCT can be considered a valid alternative option in patients whose suppression therapy fails.

Keywords: Allogeneic, Cell transplantation, Aplastic anemia, Age

1. Introduction

Aplastic anemia is a rare clinical syndrome in which there is a deficiency of red blood cells, white blood cells, and platelets, and fatty replacement of the marrow with a near-absence of hematopoietic precursor cells [1]. It primarily occurs in patients aged between 15 and 30 years; a second peak is found in the 65- to 69-year-old age group [2]. The frontline treatment for patients under the age of 40 years with severe aplastic anemia is allogeneic hematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen (HLA)-identical sibling donor [3]. Bone marrow has been shown to be superior to peripheral blood, as a stem cell source, in patients with acquired aplastic anemia undergoing a matched sibling transplant. Peripheral blood stem cells may reduce the risk of graft failure, whereas bone marrow may reduce the risk of chronic GVHD [4–6].

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Unfortunately, only about 30% of patients have an HLA-matched sibling donor, so that the use of alternative donors including mismatched related donors, cord blood, or unrelated donors has been increasingly used [7]. Immunosuppressive therapy is recommended as first-line therapy for (a) patients with severe aplastic anemia who do not have an HLA-identical sibling donor, (b) patients with severe aplastic anemia who are >35–50 years old, and (c) patients with non-severe aplastic anemia who are transfusion dependent [8]. The current standard first-line immunosuppressive regimen is a combination of horse anti-thymocyte globulin (ATG) and cyclosporine [9].

However, in patients with severe aplastic anemia who are older than 40 years, allogeneic HSCT is associated with treatment-related mortality and toxicity, even when matched sibling donors are used [10]. As a result, allogeneic HSCT in patients between 40 years and 50 years is usually only performed in specific cases. In our previous studies, outcomes of allogeneic HSCT on adult patients with paroxysmal nocturnal hemoglobinuria (PNH) and Fanconi anemia were evaluated [11,12].

It has been reported that in our patients with severe aplastic anemia between 1991 and 2011, 3-year overall survival (OS) and disease-free survival (DFS) of allogeneic HSCT was 82% and 75%, respectively [13]. In the present study, we evaluated the long-term survival rates among patients aged between 40 years and 50 years with severe aplastic anemia treated with allogeneic HSCT in the Hematology–Oncology and Stem Cell Transplantation Research Center, Tehran, Iran.

2. Materials and methods

This single-center retrospective study was performed at the Hematology, Oncology, and Stem Cell Transplantation Research Center, Shariati Hospital, Tehran, Iran, from December 2006 to December 2012. All patients with severe aplastic anemia who were 40 years or older and underwent allogeneic HSCT were included in the study.

During the study period, a total of 19 patients were assessed. All patients had full HLA-matched sibling donors, and in all of them, the source of hematopoietic stem cells was peripheral blood stem cells (PB). The conditioning regimen included intravenous (IV) cyclophosphamide (40 mg/kg/day IV on 4 consecutive days, from Days −5 to −2) and rabbit ATG (thymoglobin, 2.5 mg/kg IV once daily on 3 consecutive days from Days −5 to −3 in recipients of PB as source of hematopoietic stem cells). GVHD prophylaxis consisted of cyclosporine A and methotrexate.

OS and DFS were estimated using the Kaplan–Meier method. Univariate analysis of OS and DFS to calculate the hazard ratios (HRs) of each potential prognostic factor was performed using a Cox proportional hazard regression. Analysis was performed using SPSS Statistics software version 24 (IBM Corp., Armonk, NY, USA).

3. Results

A total of 19 patients were enrolled in this study. The basic characteristics of the study population are provided in Table 1. There were eight (42.1%) women and 11 (57.9%) men. The mean age of patients at the time of transplant was 43.79 (range, 40–50) years. The mean time from diagnosis to transplant was 840.1 (range, 90–2705) days. The estimation of the median follow-up with the reverse Kaplan–Meier method was 1916 days (95% confidence interval [CI], 1120–∞), ranging from 12 days to 4513 days.

Prior to transplantation, all patients were transfusion-dependent, 19 had anemia (hemoglobin < 10 g/dL), 18 had neutropenia (PMN < 1500/μL), and 19 had thrombocytopenia (<100,000/μL). Prior to HSCT, cyclosporine and ATG were used in four patients, and cyclosporine alone was used in 17 patients.

The observed mortality rate was 36.8% (7 cases), attributed to infection (2 cases; 10.5%), relapse (3 cases; 15.8%), and renal failure (1 case; 5.3%). The cause of death was unknown in one of the patients. Acute GVHD occurred in five patients (4 patients grade I–II and 1 patient grade III–IV), and chronic GVHD occurred in two patients (limited/mild in both patients). Graft rejection occurred in three patients (15.8%). The 5-year OS was 62% (95% CI of mean, 1963.129–3852.020; Fig. 1) and the 5-year DFS was 52% (95% CI of mean, 1504.625–3440.786; Fig. 2).

The relationship between OS and each of the dependent variables was analyzed using Cox proportional hazards regression models. In univariate analysis, significant predictors of survival were age of the patient, platelet level prior to transplantation, the number of mononuclear cells, and CD3 cells infused for each transplant. Multivariate analysis confirmed that the patient's age, platelet level prior to transplantation, and the number of CD3 cells infused for each transplant were independent prognostic factors for OS (Table 2).

In addition, prognostic factors associated with DFS in all patients were also assessed using Cox proportional hazards analysis. The results of the unilateral analysis showed that the age and sex of

Table 1. Basic characteristics of the study population.

Patient number[a]	Age (y)[b]	Sex	Prior to transplantation			Diagnosis to transplantation (d)	Acute GVHD (grade)	Chronic GVHD	Survival status	Rejection (yes/no)	Cause of death	Follow-up time (mo)
			WBC ($\times 10^9$/L)	Hb (g/dL)	Platelets (/mm^3)							
1	50	F	10	5.5	14,000	262	–	–	Dead	No	Infection	0.4
2	49	M	3.9	7	9000	2705	3	Limited/mild	Alive	No	–	85.4
3	49	F	1.9	5.3	13,000	1714	–	–	Dead	No	Renal failure/toxicity	1.4
4	49	F	8	7.2	6000	268	–	–	Dead	No	Unknown	10.4
5	47	M	7	7.6	8000	473	2	–	Alive	No	–	148.5
6	46	M	0.5	6.2	6000	181	–	–	Dead	Yes	Rejection	6.1
7	44	M	3.3	4.8	8000	90	1	Limited/mild	Alive	No	–	63.0
8	44	M	1.8	8	10,000	365	–	–	Alive	Yes	–	11.7
9[c]	43	M	1.5	7.5	15,000	1984	–	–	Dead	Yes	Rejection	5.5
10	43	F	2	4.2	5000	175	–	–	Alive	No	–	36.8
11	43	F	1.1	6.6	53,000	1919	–	–	Dead	No	Infection	0.7
12	41	F	2.1	4.3	8000	148	–	–	Alive	No	–	68.1
13	41	F	3.8	6.1	28,000	549	–	–	Alive	No	–	35.9
14	41	M	1	3.8	2000	225	–	–	Alive	No	–	99.3
15	41	M	2.5	6.5	15,000	697	–	–	Alive	No	–	58.3
16	41	M	2.5	6.6	8000	2525	1	–	Alive	No	–	32.3
17	40	M	1.5	5.3	31,000	198	1	–	Dead	Yes	Rejection	32.5
18	40	M	1.9	7.1	10,000	1226	–	–	Alive	No	–	57.5
19	40	F	2.6	7.7	20,000	258	–	–	Alive	Yes	Infection	64.4

Note. F = female; M = male; GVHD = graft-versus-host disease; Hb = hemoglobin; WBC = white blood cells.

[a] In all patients, the conditioning regimen was cyclophosphamide plus rabbit antithymocyte globulin. In all patients, the GVHD prophylaxis regimen was methotrexate plus cyclosporine A. In all patients, the source of hematopoietic stem cells was peripheral blood. All patients had full HLA-matched donors (sibling: 18 cases, other relatives: patient number 10).

[b] Age at transplantation.

[c] Rectal cancer after transplantation occurred in patient number 9.

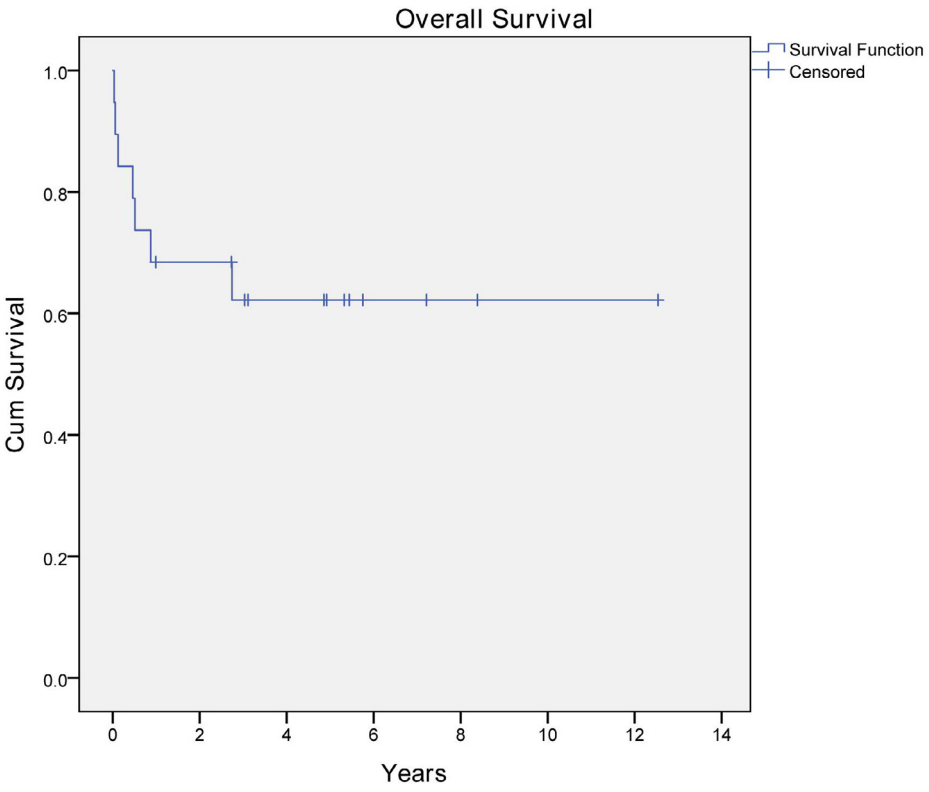

Fig. 1. Kaplan–Meier curve for Overall survival (OS) in patients with severe aplastic anemia.

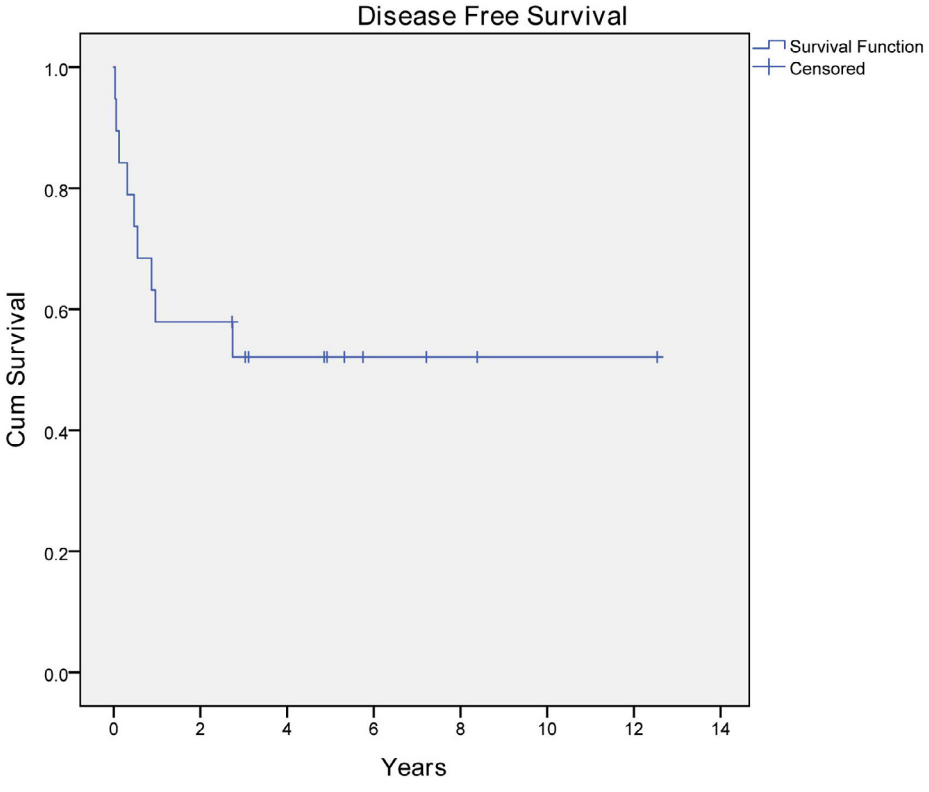

Fig. 2. Kaplan–Meier curve for Disease-free survival (DFS) in patients with severe aplastic anemia.

Table 2. Multivariable cox proportional hazards analysis of overall survival and disease-free survival.

Covariate	Overall survival				Disease-free survival			
	Univariate		Multivariate		Univariate		Mulrivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Sex	2.4 (0.53–11)	0.26	–		2.5 (0.67–9.4)	0.18*	3190 (2.73–3.72 × 10^6)	0.025**
Age	1.2 (1–1.6)	0.048*	2.10 (1.23–3.66)	0.008**	1.2 (0.97–1.4)	0.11*	10.44 (1.14–95.7)	0.038**
Rejection	2.2 (0.48–9.8)	0.31	–	–	4.5 (1.2–17)	0.029*	1.022 × 10^7 (1.59–6.54 × 10^{13})	0.043**
WBC	1.1 (0.82–1.5)	0.45	–	–	1.1 (0.79–1.4)	0.68	–	–
Hb	1.1 (0.59–1.9)	0.86		–	1.4 (0.79–2.4)	0.26	–	–
Platelet	1.1 (1–1.1)	0.058*	1.19 (1.03–1.37)	0.015**	1.1 (1–1.1)	0.046*	1.48 (1.01–2.18)	0.046**
Dx to Tx	1 (1–1)	0.57	–	–	1 (1–1)	0.9	–	–
Donor age	1 (0.96–1.1)	0.42	–	–	1 (0.97–1.1)	0.3	–	–
Nucleated WBC	0.9 (0.64–1.3)	0.55	–	–	1 (0.76–1.4)	0.78	–	–
MNC	0.71 (0.44–1.1)	0.16*	1.21 (0.46–3.2)	0.692	0.8 (0.51–1.3)	0.34	–	–
CD34	1.1 (0.86–1.4)	0.47	–	–	1.1 (0.85–1.3)	0.64	–	–
CD3	0.99 (0.99–1)	0.069*	0.99 (0.97–0.99)	0.023**	1 (0.99–1)	0.11*	0.99 (0.98–1.05)	0.71
Hospitalization	0.96 (0.85–1.1)	0.58	–	–	0.98 (0.89–1.1)	0.64	–	–
ANC engraftment	0.96 (0.84–1.1)	0.53	–	–	0.96 (0.86–1.1)	0.47	–	–
Platelet engraftment	1 (0.97–1.1)	0.5	–	–	1 (0.96–1.1)	0.71	–	–
Acute GVHD	0.5 (0.06–4.2)	0.52	–	–	0.34 (0.042–2.7)	0.31	–	–
Chronic GVHD	4.4 × 10^{-9} (0–∞)	1	–	–	4.4 × 10^9 (0–∞)	1	–	–
PC prior to HSCT	1 (0.66–1.6)	0.9	–	–	1.1 (0.72–1.6)	0.77	–	–
Platelet prior to HSCT	1.1 (0.74–1.8)	0.55	–	–	1.1 (0.77–1.6)	0.57	–	–

Note. ANC = absolute neutrophil count; CD = cluster of differentiation; Dx = diagnosis; GVHD = graft-versus-host disease; Hb = hemoglobin; HR = hazard ratio; HSCT = hematopoietic stem cell transplantation; MNC = mononuclear cell; PC = packed red blood cells; Tx = treatment; WBC = white blood cells.

* A *p*-value < 0.20 in the univariate analysis was included in the multivariate analysis.

** A *p*-value < 0.05 in the multivariate analysis was considered statistically significant.

the patient, graft rejection, platelet level prior to transplantation, and the number of CD3 cells infused for each transplant were independent predictors of DFS. Multivariate analysis revealed that the age and sex of the patient, graft rejection, and platelet level prior to transplantation were significant prognostic factors associated with DFS (Table 2).

4. Discussion

In this retrospective study, we studied the outcomes of HSCT on patients with severe aplastic anemia who were aged between 40 and 50 years in our center to have an estimation of general outcome of these diseases. Kim et al. [14] retrospectively analyzed the effect of age on transplantation outcomes and survival in 225 adult patients with aplastic anemia who underwent allogeneic HSCT: 57 patients aged >40 years and 168 patients aged ≤40 years. The favorable prognostic factors in all patients included age at HSCT of ≤40 years, time from diagnosis to HSCT of ≤6 months, and matched-related donor. The only poor prognostic factor associated with survival in elderly patients was age older than 40 years. Survival in patients younger than 50 years was not significantly different in both groups [14].

A study conducted by Giammarco et al. [15] compared the outcome of patients with severe aplastic anemia who were older than 40 years, transplanted in 2001 to 2009 ($n = 329$), with patients transplanted in 2010 to 2015 ($n = 439$). In that study, the authors showed that survival remained unchanged over the past 15 years in patients with severe aplastic anemia who were older than 40 years undergoing allogeneic HSCT. They found that the patient's age, use of either ATG or alemtuzumab in the conditioning regimen, center experience, and donor type were significant prognostic factors associated with survival. Overall, the results of this study showed that allogeneic transplants for severe aplastic anemia in patients older than 40 years have a significant risk of mortality, despite changes in conditioning regimens and donor type, and also in patients receiving an HLA identical sibling transplant [15].

It has been reported that the favorable outcome of allogeneic HSCT for patients with severe aplastic

anemia can be attributable to the use of conditioning regimen with cyclophosphamide and ATG, the use of GVHD prophylaxis with short-term cyclosporine and methotrexate, the use of irradiated blood products, and the use of a leukocyte-reduction filter at the time of transfusion [16]. The optimal conditioning regimen for aplastic anemia patients undergoing bone marrow transplantation from an HLA-matched unrelated donor is uncertain, but currently a combination of ATG and cyclosporine A is favored for older patients [17].

Graft failure or graft rejection after allogeneic HSCT is an important and life-threatening complication in patients with aplastic anemia, especially in those who have been heavily transfused. It has been found that adding total lymphoid or total body irradiation to cyclophosphamide reduced the risk of graft failure to less than 5%, but rates of secondary malignancies, interstitial pneumonia, and GVHD were higher [18]. In our center, graft rejection occurred in three patients (15.8%). In a study by Champlin et al. [19], graft failure was evaluated in 625 patients with severe aplastic anemia who underwent allogeneic HSCT from HLA-identical sibling donors. Graft failure occurred in 68 (11%) of the patients. The main factors associated with a reduced risk of graft failure included the use of radiation for conditioning regimen and use of cyclosporine or T-cell depletion for GVHD prophylaxis. The most important factors associated with improved survival included posttransplant treatment with cyclosporine as GVHD prophylaxis and avoidance of pretransplant blood transfusions. The interesting thing was that although the use of radiation in conditioning regimen reduced graft failure, it did not improve survival [19].

The cause of mortality in our study was infection (10.5%), relapse (15.8%), and renal failure (5.3%). Unlike previous studies, chronic GVHD was not the major cause of death in our study. In another study, Deeg et al. [20] evaluated 212 patients with aplastic anemia transplanted who survived more than 2 years and who were followed for up to 26 years. Lung disease occurred in 24%, bone and joint problems in 18%, skin problems in 14%, and cataracts in 12% of patients. They found that the leading cause of morbidity and mortality is chronic GVHD. The probability of survival at 20 years for patients with chronic GVHD was 69%, whereas for patients without chronic GVHD it was 89% [20].

5. Conclusion

Given the significant risk of mortality after allogeneic HSCT, immunosuppressive therapy should be considered as a first-line treatment in patients with severe aplastic anemia who are older than 40 years. We recommend that allogeneic HSCT from an HLA-identical sibling donor be considered as a valid alternative option in patients whose suppression therapy fails, although there is no sufficient evidence to routinely recommend allogeneic HSCT.

Ethical considerations

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Authors' contributions

HKF, AG, SAM, and NM devised the study concept, researched and analyzed the literature, and wrote the manuscript; MJ, SR, and DB analyzed the literature and edited the manuscript. All authors read and approved the final version of the manuscript.

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Declaration of Competing Interest

Authors declare no conflict of interest.

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