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Quality of Life in Patients with Aplastic Anemia Receiving Allogeneic Bone Marrow Transplantation

Zahid Khanzada[1], Momina Javed[2] , Tariq Ghafoor[3], Hira Tariq[4] , Raheel Iftikhar[5], Maryam Khan[6]

Department of Clinical Haematology and Bone Marrow Transplant, National University of Medical Sciences, Rawalpindi, Pakistan

Abstract

Objectives: The aim of our study is to look at the quality of life in patients who received allogeneic hematopoietic stem cell transplant from matched related donors (MRD) in a low-middle income country.
Methodology: This single-center retrospective study conducted at Clinical Hematology and Bone Marrow Transplant Department, National University of Medical Sciences, Rawalpindi, Pakistan included 68 patients who received MRD allogeneic hematopoietic stem cell transplant between 2015 and 2024. WHOQOL-BREF was used to assess quality of life. Statistical analysis was done using SPSS version 27.
Results: Median age at the time of transplant was 21.5 (range: 9-48) years consisting of 57 (83.8%) males and 11 (16.2%) females. Median $CD34^+$ stem cell dose infused was 4.98 (range: 1.53–14.58) × 10^6 cells/kg. Neutrophil and platelet engraftment were achieved on median of day +13 (range: 9–25) and day +22 (range: 14–71) respectively. Most frequent complications included cytomegalovirus reactivation in 21 patients (30.9%) and graft-versus-host disease (Grade II-IV/Extensive) in 19 patients (27.9 %). Median duration from transplant to day of assessment of quality of life was 2573 (range: 386-4992) days. Mean quality of life scores were86.13 (±18.42) in physical, 82.04 (±19.65) in psychological, 75.73 (±18.36) in social relations and75.14 (±17.71) in environmental domains. Increasing recipient age showed a negative correlation with quality of life scores in physical ($r = -0.2$, $p < 0.05$), psychological ($r = -0.1$) and environmental ($r = -0.2$) domains. Increasing donor age had negative impact on recipient's quality of life in all domains while statistical significance was seen only in environmental domain ($r = -0.2$, $p < 0.05$). Male recipients reported significantly higher psychological ($p = 0.01$) and environmental ($p = 0.01$) scores, with better scores in physical ($p = 0.12$) and social relations ($p = 0.37$) domains. Recipients who received bone marrow harvest alone exhibited superior quality of life scores in physical ($p=0.44$), psychological ($p=0.93$) and social relations ($p = 0.02$) compared to peripheral blood stem cells or a combination of both. Chronic graft-versus-host disease had significant adverse impact on quality of life in physical ($p = 0.07$) domain with lower scores in psychological ($p = 0.48$), social relations ($p = 0.33$) and environmental ($p = 0.0.34$) domains as well. Patients with cytomegalovirus reactivation had significantly worse psychological scores ($p = 0.03$) and physical ($p = 0.06$) and environmental ($p = 0.06$) scores.
Conclusion: Allogeneic hematopoietic stem cell transplant is curative therapeutic option for aplastic anemia and patients report good long-term quality of life. Younger recipient age, male gender and bone marrow harvest as the stem cell source were associated with better quality of life. Chronic graft versus host disease is a major detriment to quality of life, underscoring the need for chronic GVHD prevention and management strategies.
Key words: Quality of life, Aplastic anemia, bone marrow transplant, allogeneic hematopoietic stem cell transplant

Address for Correspondence
Dr Zahid Khanzada,
Department of Clinical Haematology and Bone Marrow Transplant, National University of Medical Sciences, Rawalpindi
zahidkhanzada13@gmail.com

Introduction

Acquired Aplastic anemia (AA) is an immune-mediated disorder characterized by pancytopenia with a hypocellular bone marrow with no evidence of abnormal infiltrate or marrow fibrosis.[1] Standard first-line treatment for newly diagnosed severe aplastic anemia (SAA) patients is allogeneic hematopoietic stem cell transplant (allo-HSCT) in presence of a suitable donor and horse anti-thymocyte globulin (hATG), ciclosporin and eltrombopag for patients lacking a donor.[1-3] Allo-HSCT is the only curative treatment for AA with a long term survival ranging from 70-90%.[4] However, Allo-HSCT can be complicated with graft versus host disease (GVHD), infections and long term complications (hormonal abnormalities, osteoporosis, and infertility) which may impact quality of life (QoL) among allo-HSCT survivors.[4] World Health Organization (WHO) definition of quality of life is an individual's perception of their position in life in

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context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[5] Most published transplant studies focus on GVHD, overall survival (OS), treatment related mortality (TRM) and disease free survival (DFS). Data on quality of life (QoL) in patients receiving Allo-HSCT for AA is lacking. The aim of our study is to look at the quality of life in patients who have undergone Allo-HSCT from Matched related donors in a low-middle income country.

Methodology

This single-center retrospective study was conducted at Clinical Hematology and Bone Marrow Transplant Department of National University of Medical Sciences, Rawalpindi Pakistan. The study was approved by the hospital ethics committee and adhered to the principles of the Declaration of Helsinki. This was a census-based, cross sectional analytical study that included68 patients who receive dallo-HSCT between 2015 and 2024. Data of all the patients who received allo HSCT from HLA matched related donor at our institute from 2015 to 2024 was reviewed. Patients age >15 years and at least 1 year since day of transplant were included while those who did not consent to participate in this study were excluded. Contacted patients were invited to fill out the WHOQOL BREF 26 questionnaire at hospital long term follow-up clinic. Those who were unable to come to hospital to fill the form were sent the questionnaire by mail to fill and return. All of the previous data was obtained from hospital records and entered in SPSS along with QOL data.

Instrument description and scoring: The WHOQOL-BREF was used for QoL assessment that has 26 questions consisting of four domains: social relationships, physical, psychological and environmental health. Every answer is scored from 1 to 5 on a response scale, where 1 is strong disagreement and 5 is strong agreement to given statement. Items 3, 4 and 26 were recorded negatively and then converted to normal scale. For uniform comprehension, the form was translated in Urdu and each question explained in detail to every participant. Translated version from WHO website was used.[5]

Statistical analysis of data was done using SPSS version 27. Percentage and frequencies of qualitative variables were documented including mean and standard deviations of quantitative variables.

Results

The cohort comprised of 68 patients having acquired AA with median age at the time of transplant 21.5 (range: 9-48) years consisting of 57 (83.8%) males and 11 (16.2%) females. Majority of patients had severe AA 41 (60.3%), followed by very severe AA 18 (26.5%) and non-severe AA 6 (8.8%). Disease severity of 3 (4.4%) patients was not available. Fifty-eight patients (85.3%) were found to have no PNH clone. Forty-nine patients (72.1%) had no comorbidities at the time of transplant. In this cohort, 37 patients (54.4%) received upfront Allo-HSCT without prior IST. The remaining patients received IST before Allo-HSCT: 18 patients (26.5%) with cyclosporine monotherapy, 4 patients (5.9%) with cyclosporine and eltrombopag, 1 patient (1.5%) with eltrombopag monotherapy, and 2 patients (2.9%) with cyclosporine and mycophenolate mofetil.

All patients in the cohort received fully HLA matched Allo-HSCT. The majority of donors were brothers (46, 67.6%), followed by sisters (19, 27.9%), first cousins (2, 2.9%), and one mother (1, 1.5%). Out of 68 patients, 41 (60.3%) had no ABO mismatch, 10 (14.7%) had major, 10 (14.7%) had minor while bidirectional mismatch was in 7(10.3%) patients. The most prevalent stem cell source in this study was a combination of bone marrow and peripheral blood stem cells (PBSC) in 36 patients (52.9%), followed by bone marrow harvest alone in 30 patients (44.1%), and PBSC alone in 2 patients (2.9%). A total of 29 patients (42%) received a conditioning regimen comprising fludarabine 150 mg/m², cyclophosphamide 120 mg/kg, and anti-thymocyte globulin (ATG) 20 mg/kg ($Flu^{150}Cy^{120}ATG^{20}$), while another 29 patients (42%) received fludarabine 120 mg/m², cyclophosphamide 120 mg/kg, and ATG 20 mg/kg ($Flu^{120}Cy^{120}ATG^{20}$). The median $CD34^+$ stem cell dose infused was 4.98 (range: 1.53–14.58) × 10^6 cells/kg. Neutrophil engraftment was achieved at a median of day +13 (range: 9–25), while platelet engraftment occurred at a median of day +22 (range: 14–71).

The most frequent complications included cytomegalovirus (CMV) reactivation in 21 patients (30.9%) and graft-versus-host disease (GVHD grade II-IV/Extensive) in 19 patients (27.9 %). Erythrocytosis requiring phlebotomy occurred in 17 patients (25.0%), hemorrhagic cystitis in 15 (22.1%), and platelet refractoriness in 13 (19.1%). Chronic GVHD was seen in 9 patients (13.2 %), serum sickness in 9 (13.2%), and acute

GVHD in 5 (7.4 %). Overlap syndrome (both acute and chronic GVHD) was reported in 2 patients (2.9%), while 3 patients (4.4 %) had both acute and chronic GVHD.

Other complications included mucositis in 5 patients (7.4%), pure red cell aplasia (PRCA) in 5 (7.4%), herpes reactivation in 5 (7.4%), and fungal infections in 4 patients (5.9%). Tuberculosis reactivation was noted in 4 patients (5.9%), veno-occlusive disease (VOD) in 2 (2.9%), and engraftment syndrome in 2 (2.9%). Secondary graft failure was observed in 5 patients (7.4%), while no cases of primary graft failure were reported. Four patients (5.9%) received stem cell boosts due to secondary graft failure.

Median duration from transplant to day of assessment of quality of life was 2573 (range: 386-4992) days. Average QoL scores are shown in Table I. Lowest score is noted in Environmental and Social relations domain.

Table I: Quality of life scores.

Questionnaire Dimensions	QoL Score (mean ± std)	min-max
Physical	86.13 ± 18.42	14.29 - 100
Psychological	82.04 ± 19.65	16.67 - 100
Social Relation	75.73 ± 18.36	25 - 100
Environmental	75.14 ± 17.71	25 - 100

The correlation of QoL scores with described factors are shown in Table II and the relationship of QoL scores with transplant related factors is shown in Table III.

Recipient's age showed a negative correlation with QoL scores in physical ($r = -0.2$, $p < 0.05$), psychological ($r = -0.1$) and environmental ($r = -0.2$) domains. Increasing donor age had negative impact on recipient's long term QoL in all domains while statistical significance was seen only in environmental domain. Time duration from diagnosis to allo-HSCT, disease severity, PNH clone, number of RCC and platelet transfusions, Serum ferritin, TNC (Total nucleated cells) /MNC (Mononuclear cell dose) /CD34 dose, day of neutrophil engraftment, conditioning protocol, ABO mismatch, VOD, secondary graft failure, PRCA and post-transplant erythrocytosis (PTE) showed no significant correlation with QoL while day of platelet engraftment had weak correlation with no statistical significance. Male recipients reported significantly higher psychological ($p = 0.01$) and environmental ($p = 0.01$) scores compared to females, with trends towards better physical ($p = 0.12$) and social relations ($p = 0.37$) domains.

Recipients who received BMH alone as a stem cell source exhibited superior QoL scores in physical ($p=0.44$), psychological ($p=0.93$) and social relations ($p = 0.02$) compared to PBSC or combined BMH+PBSC. GCSF priming of donors had adverse effect on recipient's QoL in psychological ($p = 0.05$), social relations ($p = 0.01$), physical ($p = 0.12$) and environmental ($p = 0.21$) domains. Chronic GVHD was associated with markedly lower QoL scores across all domains. Patients suffering from acute GVHD showed non-significantly higher physical and psychological scores in long term follow-up. Patients with CMV reactivation had significantly worse psychological scores ($p = 0.03$) and trends toward lower physical ($p = 0.06$) and environmental ($p = 0.06$) scores.

Discussion

This single-center analysis demonstrates that allogeneic hematopoietic stem cell transplantation (allo-HSCT) provides good long-term quality of life (QoL) in aplastic anemia (AA) patients, with long-term survivors achieving transfusion independence and resumption of

Table II: The correlation of QoL scores with transplant related factors.

	Physical r	Psychological r	Social Relations r	Environmental r
Patients' Age	-0.2*	-0.1	0	-0.2
Donors' Age	-0.1	-0.1	-0.1	-0.2*
Time to transplant	0	0	0	0
RCC transfusion pre-HSCT	0	-0.1	0	0
Platelet transfusion pre-HCT	0	0	0	0
Serum ferritin	-0.1	0	0.1	0
TNC	0	0	-0.1	0
MNC	0	-0.1	0	0
CD 34 +	0	0	-0.1	0.1
Day+ of Neutrophil Engraftment	-0.1	0	0	-0.1
Day+ of Platelet engraftment	-0.1	-0.1	0.1	-0.1

*Note: Pearson correlation test was applied, r = correlation, * Correlation is significant at the 0.05 level.*

Table III: The relationship of quality of life scores with transplant related factors.

		Physical		Psychological		Social relations		Environmental	
		Mean	p-value	Mean	p-Value	Mean	p-Value	Mean	p-Value
Gender	Male	87.66	0.12	84.65	0.01	76.61	0.37	77.58	0.01
	Female	78.25		68.56		71.21		62.50	
Severity	Non severe	89.29	0.68	88.89	0.75	77.78	0.89	76.05	0.83
	Severe	84.06		81.71		75.20		74.85	
	Very severe	88.49		79.63		75.00		76.91	
	Not available	94.05		87.50		83.33		66.67	
PNH Clone	Absent	86.45	0.71	82.26	0.57	76.44	0.29	75.38	0.90
	Present	84.29		80.83		71.66		73.75	
IST	CSA	91.47	0.37	89.35	0.71	83.33	0.06	75.00	0.61
	CSA and Eltrombopag	69.65		67.71		72.92		58.60	
	Eltrombopag	89.29		87.50		75.00		84.38	
	CSA and MMF	75.00		62.50		58.34		81.25	
	CSA and Methyprednisolone	71.43		66.67		75.00		71.88	
	CSA and Prednisolone	67.86		37.50		25.00		59.38	
	Not available	92.86		86.46		70.83		71.88	
	No IST used	86.00		82.09		75.22		77.28	
Source of stem cells	BMH	89.29	0.44	83.06	0.93	82.22	0.02	74.69	0.97
	PBSC	80.36		81.25		79.17		73.44	
	BMH+PBSC	83.83		81.25		70.14		75.61	
BM priming	Yes	81.62	0.12	78.35	0.05	71.14	0.01	72.94	0.21
	No	92.99		87.65		82.72		78.47	
ABO mismatch	No ABO mismatch	85.28	0.42	83.43	0.18	79.27	0.12	73.71	0.21
	Minor ABO mismatch	93.57		83.75		73.33		83.44	
	Major ABO mismatch	80.36		70.00		64.17		68.75	
	Bidirectional ABO mismatch	88.78		88.69		75.00		80.81	
Conditioning protocol	Flu150, Cy120, ATG20	82.51	0.50	79.02	0.71	73.28	0.26	73.39	0.65
	Flu120, Cy120, ATG20	87.69		84.77		75.57		76.40	
	Flu120, Cy160, ATG20	100.00		84.72		97.22		85.42	
	Flu120, Cy120, TG10	64.29		54.17		75.00		59.38	
	Flu150, Cy120, TG10	100.00		79.17		91.67		53.13	
	Cy200, TG10	91.07		88.54		81.25		81.25	
	Cy200, ATG20	92.86		87.50		50.00		71.88	
GVHD Prophylaxis	CSA	90.72	0.47	82.33	0.99	80.00	0.42	77.63	0.48
	CSA + MTX	83.93		83.10		77.31		71.36	
	CSA + MMF	84.07		81.41		71.79		78.37	
	CSA + MTX + MMF	78.97		80.55		67.59		75.70	
	CSA + Prednisolone	91.67		80.55		72.22		61.46	
Graft failure	Yes	85.72	0.96	75.00	0.52	77.78	0.84	69.80	0.59
	No	86.15		82.37		75.64		75.39	
VOD	Yes	89.29	0.97	66.67	0.53	83.34	0.84	82.82	0.50
	No	86.05		82.55		75.52		75.30	
	Not Available	85.72		81.25		75.00		62.50	
CMV reactivation	Yes	79.93	0.06	74.60	0.03	74.21	0.65	69.20	0.06
	No	88.91		85.37		76.42		77.80	
PRCA	Yes	85.00	0.88	75.00	0.40	61.67	0.07	75.00	0.98
	No	86.23		82.61		76.85		75.15	
GVHD	Acute	97.14	0.07	92.50	0.48	85.00	0.33	78.75	0.34
	Chronic	76.59		73.61		73.15		65.62	
	Overlap	98.21		89.58		58.34		75.00	
	No GVHD	87.39		82.48		76.70		77.17	
	Acute + Chronic	67.85		77.78		63.89		64.58	
PTE	Yes	83.19	0.45	81.13	0.82	76.96	0.75	75.00	0.97
	No	87.11		82.35		75.33		75.19	

Note: One way- Anova test was applied, p-value less than 0.05 was considered significant.

normal lifestyle. These findings position allo-HSCT as a curative intervention with good long term QoL metrics.

Our observations align with prior studies reporting favorable QoL outcomes post-allo-HSCT, specifically, our data corroborate findings by Meiqing Li et al. (2023).[6]

In comparison to patients treated with immunosuppressive therapy (IST) reported by P. Escalante et al. [7], Ting Leu et al. [8], and Chen FF et al. [9], our cohort reported better QoL metrics. This reinforces the paradigm that allo-HSCT offers dual advantages—curative potential and good long-term life quality.

Multivariate analysis identified several clinically significant predictors of QoL like recipient age, donor age, recipient gender, source of stem cells, CMV reactivation, cGVHD and G-CSF priming of donors.

Younger recipients exhibited significantly better QoL, similar findings were also reported by Meiqing Li et al.[6], Olga Zając-Spychała et al. [10] and S. Chiodi et al. [11]

Recipients of grafts from younger donors had higher overall QoL scores. Multiple studies have shown older age of donors resulted in higher rates of complications like GVHD but there are no studies focusing specifically on QoL metrics.[12-15]

Male recipients exhibited significantly better QoL scores in all domains, these findings were similar to gender-associated disparities observed by H. Heinonen et al. [16], J M Prieto et al. [17], Shinichiro Morishita et al. [18], Pablo Ortolá-Alonso et al.[19] and OzlemOvayolu et al. [20]

In contrast to the study by Zheng-Li Xu et al.[21], which reported that a longer duration disease from diagnosis to allo-HSCT negatively impacted long term QoL, our analysis revealed no such correlation.

Chronic GVHD significantly diminished QoL scores in all domains, consistent with multiple previous studie·[11,22-31] Recipients who received BMH alone as compared to patients who received PBSC or combination of BMH and PBSC as a source of stem cells reported better QoL. Patients who received PBSC had a higher rate of cGVHD and this finding maybe attributed higher rates of cGVHD in patients who received PBSC as observed in multiple previous studies.[32-35] Post-transplant erythrocytosis (PTE) had no significant impact on QoL and this has not been documented in the past.

A previously unreported association emerged between donor G-CSF priming and reduced recipient QoL, particularly in psychological ($p = 0.01$) and social ($p = 0.02$) domains. This can be attributed to higher use of PBSC in GCSF primed marrows which in turn caused higher rates of cGVHD.

This study has several limitations including absence of baseline QoL data, precluding longitudinal assessment of post-HSCT improvement and sample size constraints, which may limit statistical power for subgroup analyses.

Conclusion

Allo-HSCT not only serves as a curative treatment for aplastic anemia (AA) but patients reportgood long-term quality of life (QoL), enabling transfusion independence and a return to normal daily activities.

Younger recipient age, male gender and BMH as the stem cell source were associated with better QoL, whereas donor age, time to transplant, disease severity, PNH clone,

CD34/TNC/MNC dose, pre-transplant serum ferritin, and post-transplant erythrocytosis showed limited or no significant impact. Notably, chronic GVHD emerged as a major detriment to QoL across all domains, underscoring the need for chronic GVHD prevention and management strategies.

These results advocate for allo-HSCT as the preferred therapeutic approach in eligible AA patients, given its dual benefits of disease cure and good long term life quality. Future studies should explore strategies to mitigate GVHD and further optimize transplant protocols to maximize long-term patient well-being.

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