Internal Medicine Section

Impact of Blood Transfusion on Haematopoietic Stem Cell Transplantation Outcome

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ABSTRACT

Introduction: Allogeneic Haematopoietic Stem Cell Transplantation (AHSCT) is a potentially curative therapy for many haematological malignancies. Nearly all patients who undergo AHSCT require frequent transfusion of blood products until Red Blood Cells (RBCs) and platelet engraftment occur. However, blood transfusion has seldom been studied as a risk factor for adverse post-transplant outcome.

Aim: To investigate the impact of blood transfusion on post-transplant outcome.

Materials and Methods: This single-center retrospective study, analysed the data of 50 adult patients with haematological malignancies who had received AHSCT, regarding the incidence of infection, acute and chronic Graft Versus Host Disease (GVHD) and overall survival, for one year after AHSCT. The collected data was divided into two groups according to the amount of transfused RBCs and platelet units; the low transfusion group (<10 units, n=30) and high transfusion group (>10 units, n=20).

Results: The incidence of infectious episodes and GVHD development were significantly higher among the high transfusion group than that in low transfusion group (p=0.006) and (p=0.02), respectively. In the low transfusion group, the incidence of acute GVHD was 3.3% and of the chronic GVHD was 3.3% while in high transfusion group, the incidence of acute GVHD was 15% and of chronic GVHD was 20%. The overall survival was significantly lower in the high transfusion group 25% than that in the low transfusion group, 46.7% (p=0.02) during the first year post-transplant.

Conclusion: Data from the present study indicate that higher transfusion history was associated with increased risk of infection, development of GVHD and worse overall survival in patients who received AHSCT. Thus, new rational for improving transfusion practice based on symptoms driven criteria for such patients is highly warranted.

INTRODUCTION

AHSCT is a curative treatment for many malignant and non-malignant haematologic disorders such as aplastic anaemia/marrow-failure states plus a continuously expanding list of auto-immune, inherited metabolic and immuno-deficiency diseases [1].

The outcome of patients receiving AHSCT is measured in terms of overall survival and disease-free survival. These endpoints represent a summary of many events related to GVHD, treatment related complications and disease relapse [2]. Patients receiving HSCT require essential RBC and platelet transfusion support until engraftment occurs and sufficient haematopoiesis is achieved in all lineages. The requirement criteria of transfusion support for patients receiving HSCT as regard to duration, frequency and type of blood products needed are variable depending on several factors such as the nature of the disease, the source of the stem cells, the conditioning pre-transplant regimen, and patient factors during the post-transplantation period [3,4].

A transfusion threshold at a Hb level of 7 or 8 g/dL is well accepted among transplant centers, which mirrors the current AABB guidelines for critically ill, hospitalised patients while platelet transfusions is minimised by adhering to evidence-based guidelines, using a platelet count of 10,000/μL as a threshold for administering platelets to a non-bleeding patients [4]. Transfusion related complications are more frequently seen in the patient population receiving AHSCT. Standard transfusion reactions, such as allergic or febrile non-haemolytic reactions, are frequently seen in this heavily transfused patient population [5]. Some of these complications occur due to activation of the lymphocytes within the transplant against the recipient, leading to Transfusion Associated Graft Versus Host Disease (TA-GVHD) and Passenger Lymphocyte Syndrome (PLS) [6]. Logan AC et al., performed a retrospective, multivariate analysis that showed among patients who underwent AHSCT, ABO mismatch between allo-HSCT donor and recipient has been associated with an increased risk of GVHD in some patient populations, however not in others [7].

In addition, blood transfusion related iron overload, is commonly seen in those patients undergoing HSCT. Several previous studies have documented the adverse prognostic impact of iron overload in such patients as it increases the risk of acute GVHD, the incidence of blood stream infections and sinusoidal obstruction syndrome of the liver [8]. However, the prognostic impact of blood transfusion on the post-transplant outcome was seldom investigated.

Here, the aim of this study was to evaluate the impact of RBC and/or platelet transfusion on the incidence of infection, risk of development of acute and chronic GVHD and overall survival in patients undergoing AHSCT.

MATERIALS AND METHODS

The present study was conducted on 50 adult patients with primary malignant haematological diseases who achieved complete remission and underwent AHSCT from fully Human Leucocyte Antigens (HLA) matched sibling donor at Ain Shams university bone marrow transplantation unit, between 2015 to 2018.

A retrospective analysis was done for the clinical and laboratory data of included patients to explore the impact of amount of transfused units of blood products on post-transplantation sequels.

The study excluded the data of patients who had any of the following conditions: patients in relapse or partial remission, patients with platelet refractoriness, patients with ABO mismatched AHSCT, patients who did not achieve complete chimera (>90% donor cells) before day 30 or engraftment (neutrophil count >0.5x 10^9 /L) up to

day 35, patients whose disease relapsed until day 60 and patients who did not survive until day 100.

The research protocol for data analysis of this study was reviewed and approved by Ain Shams University Ethical Committee for research and it was in accordance with the 1964 declaration of Helsinki and its later amendments. Written informed consent was obtained from all included patients in the study.

Patients Criteria

Diagnosis of 50 included patients varied between Acute Myeloid Leukaemia (AML), Acute Lymphoblastic Leukaemia (ALL), biphenotypic acute leukaemia, and high risk Myelo Dysplastic Syndrome (MDS). Patients with AML and high risk MDS were given Conditioning regimens pre-transplant included fludarabine/busulphan protocol. It was constituted of fludarabine 30 mg/m^2/day IV (day-6 to -3), busulphan 1 mg/kg/6 hours orally (day-6 to -3) and patients with biphenotypic acute leukaemia received fludarabine/busulphan/cytosine arabinoside /vepeside protocol which is composed of five days of intravenous fludarabine at a dose of 30 mg/m^2/day (day -6 to -2), cytosine arabinoside given at a dose of 1200 mg/m^2/day intravenously (at day -6 and -5), busulphan at a dose of 4.5 mg/kg/day (at day -4 and -2) orally, and etoposide at a dose of 6 mg/kg/day intravenously (from day -6 to day -2), while patients with ALL received TBI/cyclophosphamide protocol, constituted of fractionated 12 Gray TBI over 3 days followed by cyclophosphamide 120 mg/kg over 2 days as a pre-transplant conditioning regimen.

The data of the selected patients were divided in two groups according to the amount of transfused units of blood products, Group (I) low transfusion group including 30 patients who received less than 10 units and Group (II) the high transfusion group including 20 patients who received more than 10 units.

RBC and Platelet Transfusions Criteria

All RBC and platelet units were irradiated and RBCs were used within 28 days of irradiation. All transfused units were provided by Ain shams university hospital blood bank. Transfusion threshold for one platelet apheresis unit was platelet count <10,000/μL or at the time of bleeding. While the transfusion threshold for 2 RBCs units was haemoglobin level 7-8 gm/dL or in case of haemorrhage-induced anaemia to maintain haemoglobin level >8 gm/dL. No erythropoiesis stimulating agents were used in these patients.

Methodology and Study Endpoint

In this retrospective study, all relevant data were gathered from patients records during the first year after AHSCT, the collected data included the number and type of units received (Packed RBCs or platelets) and the time of receiving the transfusion with respect to transplantation. Also, patient records during post-transplant period were reviewed with regards to development of Infectious episodes (bacterial, viral, parasitic or fungal) other than neutropenia, development of GVHD (either acute or chronic, time of presentation, type of presentation) and overall survival time.

STATISTICAL ANALYSIS

Data were analysed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean±Standard Deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-samples t-test of significance was used when comparing between two means. Chi-square (χ^2) test was used to compare proportions between two qualitative parameters; p-value>0.05 non-significant, p≤0.05 significant, p≤0.01 highly significant. A Kaplan-Meir curve was plotted to calculate the cumulative survival time.

RESULTS

A total of 50 patients data were included; there were 26 males and 24 females with an age range between 17 and 60 years. The mean age of group 1 was 35.1±12.85 and of group 2 was 35.3±11.85. Insignificant differences were found between both groups regarding age, gender, primary malignant haematological disease, pre-transplant conditioning regimen and GVHD prophylaxis regimen.

Regarding the type of units used, 3 out of 30 patients (10%) in group 1 needed only RBCs, 7 patients (23.3%) needed only platelet transfusion and 10 patients (33.3%) needed both platelet and packed RBCs. While in group 2, all patients (100%) needed transfusion of both blood components with significant differences (p<0.001) [Table/Fig-1].

Type of units	Group I (<10 units) (N=30)		Group II (>10 units) (N=20)		Chi-square test	
	No.	%	No.	%	χ^2	p-value
Non	10	33.3%	0	0.0%	9.706	<0.001
RBCs	3	10.0%	0	0.0%	1.404	0.236
PLTS	7	23.3%	0	0.0%	5.810	0.016
RBCS+PLTS	10	33.3%	20	100.0%	27.097	<0.001

[Table/Fig-1]: Comparison between groups according to type of units.
Non: Patients with no transfusion requirements; PLTS: Platelets transfusion; RBCs: packed Red blood cells transfusion

Impact of Blood Transfusion on Development of Infection

Twenty four patients out of 50 (48%) experienced a total of 30 infectious episodes during a period of one year after transplant. Group 1 patients experienced 43.3% of the total infectious episodes while 56.7% of infectious episodes experienced by group 2 patients. There was a statistically significant difference between the two groups in developing infections p=0.006. There was a statistically significant difference between the groups according to incidence of viral HBV [Table/Fig-2,3].

Infection	Group I (<10 units) (N=30)		Group II (>10 units) (N=20)		Chi-square test	
	No.	%	No.	%	χ^2	p-value
Non	20	73.3%	6	30.0%	7.457	0.006
Bacterial	2	6.7%	2	10.0%	0.014	0.915
Viral-HCV	1	3.3%	2	10.0%	0.274	0.601
Viral-HBV	2	6.7%	6	30.0%	3.991	0.046
Viral-CMV	1	3.3%	1	5.0%	0.191	0.662
Fungal	1	3.3%	0	0.0%	0.046	0.829
Bacterial+Viral-HCV	1	3.3%	1	5.0%	0.191	0.662
Bacterial+Viral-HBV	1	3.3%	0	0.0%	0.046	0.829
Viral-HCV+Fungal	0	0.0%	1	5.0%	0.042	0.837
Viral-CMV+Fungal	1	3.3%	1	5.0%	0.191	0.662

[Table/Fig-2]: Comparison between groups according to infection.
Non: Patients with no infectious episodes

Impact of Blood Transfusion on Development of GVHD

Of the 50 patients who achieved donor engraftment, the number of patients who did not developed GVHD was 28 out of 30 in group 1 (93.3%) and 13 out of 20 in group 2 (65%), with a significant difference (p=0.029) but there was no significant difference between the two groups regarding the organs affected. Acute GVHD developed in one of 30 patients (3.3%) in group 1 and 3 of 20 (15%) in group 2. Patients who achieved durable engraftment and survived for 100 days, chronic extensive GVHD developed in one patient (3.3%) in the low transfusion group and 4 of 20 (20%) in the higher transfusion group [Table/Fig-4,5].

Impact of Blood Transfusion on Overall Survival

Both groups showed a variable difference in overall survival in first year post-transplant. The first year survival was 46.7% in group
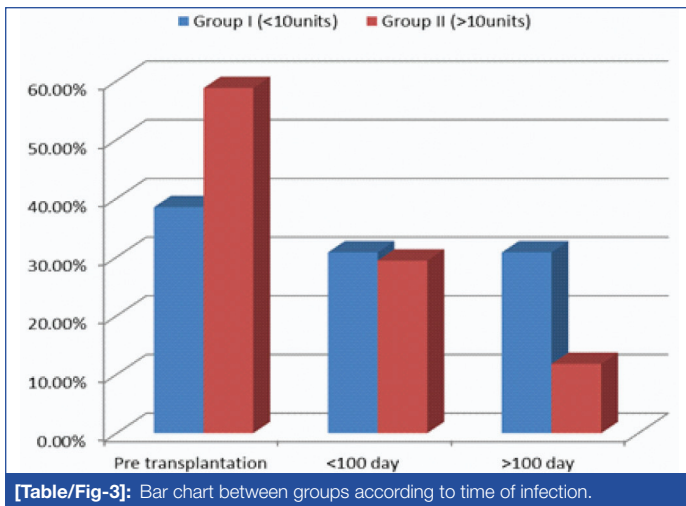
[Table/Fig-3]: Bar chart between groups according to time of infection.

GVHD	Group I (<10 units) (N=30)		Group II (>10units) (N=20)		Chi-square test	
	No.	%	No.	%	χ^2	p-value
Non	28	93.3%	13	65.0%	4.731	0.029
GIT	0	0.0%	2	10.0%	1.063	0.302
Liver	1	3.3%	1	5.0%	0.191	0.662
Skin+GIT	1	3.3%	2	10.0%	0.137	0.711
Liver+GIT	0	0.0%	1	5.0%	0.042	0.837
Skin+GIT+liver	0	0.0%	1	5.0%	0.042	0.837

[Table/Fig-4]: Comparison between groups according to GVHD.

Type of GVHD	Group I (<10 units) (N=30)		Group II (>10 units) (N=20)		Chi-square test	
	No.	%	No.	%	χ^2	p-value
Acute	1	3.3%	3	15%	0.927	0.335
Chronic	1	3.3%	4	20%	2.098	0.148
No	28	93.3%	13	65%	4.732	0.029

[Table/Fig-5]: Comparison between groups according to type of GVHD.

1 and 25% in group 2 with a significant difference (p=0.021). No statistically significant difference was found between groups according to median of survival (two years) however low transfusion group still had increased survival [Table/Fig-6,7].
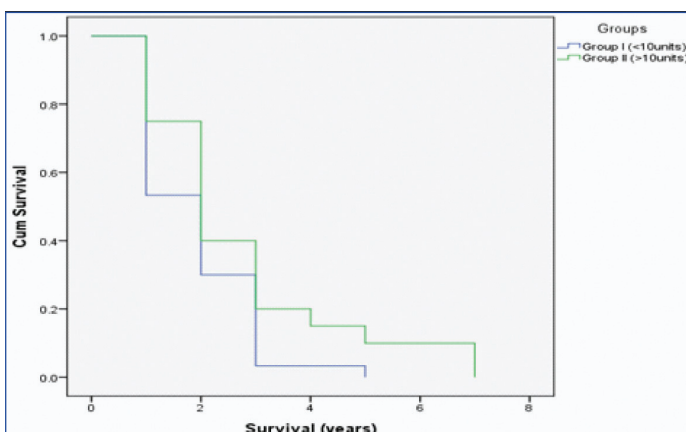
[Table/Fig-6]: Kaplan-Meir curve: Survival between group I and group II.

	Survival	Median estimate	Std. error	95% C.I.		Chi-square	Sig.
				Lower	Upper		
Group I (<10 units)	53.3%	2.00	0.23	1.45	2.35	2.007	0.098
Group II (>10 units)	40.0%	2.00	0.31	1.39	2.61		
Overall	48.0%	2.00	0.24	1.53	2.47		

[Table/Fig-7]: Survival between group I and group II.

DISCUSSION

Despite advances in transplantation practice, morbidities and mortality remains a major hurdle to improving HSCT outcome [9]. In light of the fact that the impact of blood transfusion on clinical outcomes in patients undergoing AHSCT is still poorly understood. This study was done to gain more insight and knowledge about the association between the number of RBC and /or platelet units transfused with the incidence of infection, development of GVHD and overall survival. The current study found that the incidence of developing infection was significantly higher among the high transfusion group (60% of this group experienced at least one infectious episode during the investigated period) than that in the low transfusion group (p=0.006) which may be attributed to transfusion transmitted infection and the state of transfusion induced iron overload that increase the risk of blood stream infection.

Many previous studies were in agreement with the current study as they found that the total volume of RBC and platelet units transfused positively correlated with the infection rate (p<0.05) and restriction of transfusion in HSCT patients is associated with a lower incidence of infection than in patients with high transfusion burden and they attributed their finding to the iron overload in such patients [10,11]. The present study found a significant difference between the high and low transfusion groups regarding the incidence of Hepatitis B virus (HBV) which was higher in the high transfusion group (30%) than in the low transfusion group (6.7%). Furthermore, the incidence of Hepatitis C virus (HCV) was also higher in the high transfusion group 10% than in low transfusion group 3.3%. The incidence of HBV and HCV was higher in the index study than the results reported by Francisci D et al., who found that the prevalence of HBV was 15.6% and that of HCV was 3.7% in patients undergoing AHSCT [12]. While in the current study, the incidence of CMV was 6.6% in low transfusion group and 10% in high transfusion group with no significant difference between the two groups. A higher incidence was reported by Slade M et al., who found the incidence of CMV infection was (15%) and higher incidence of viremia was observed [13].

The results of the present study demonstrated that the incidence of GVHD was significantly higher in high transfusion group than in low transfusion group. The incidence of both acute GVHD and chronic GVHD were higher in high transfusion group, these results were comparable to other published results by Lee S et al., who found that the number of pre-transplantation RBC transfusions was associated with aGVHD in AHSCT patients and they suggest that these results are due to the iron overload state in high transfusion group [14]. Another study by Hosoba S et al., who demonstrated positive association between the number of RBC units transfused with the incidence of severe aGVHD in patients undergoing AHSCT however they attributed that the increased incidence of development of aGVHD to the associated anaemia [15]. This association of RBC transfusions with aGVHD was also agreed by Hendrickson JE et al., who thought that transfused RBCs increase co-stimulatory molecules on recipient APCs, leading to increased activation of donor T-cells and increased aGVHD [16].

In this study, the overall survival was significantly higher in low transfusion group (46.7%) than that in high transfusion group (25%) during the first year post-transplant. Alessandrino EP et al., also found that there was an inverse correlation between transfusion burden and overall survival after transplantation (p=0.022). Furthermore, they documented a positive correlation between transfusion burden and non-relapse mortality (p=0.024) and the outcome of transplanted patients, who received more than 20 red cell units were significantly worse [17]. In another study Hosoba S et al., demonstrated that increased numbers of transfused RBC units (HR per 2 units =1.17, p<0.0001) was also associated with worse long-term survival in univariable analysis and they attributed this results to demonstrate significant association of RBC transfusions with the subsequent development of grade III-IV aGVHD [18].

LIMITATION

This study had a number of limitations related to its retrospective nature and lack of serum ferritin data for the transplanted patients. Second, because the included patients had different types of haematological malignancies and received different pre-transplant conditioning regimen which would affect their transfusion requirements, disease free survival and overall survival, however if the patients were divided into many subgroups according to the primary disease, that would have affected the statistical power of the study.

CONCLUSION

The data presented in the current study has highlighted the adverse impact of high transfusion burden on the AHSCT outcome as regard to the overall survival and post-transplant complications. Thus, new rationale for more restricted transfusion practice based on symptoms driven criteria for these patients is highly warranted.

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REFERENCES

[1] Okamoto S. Current indication for hematopoietic cell transplantation in adults. Hematol Oncol Stem Cell Ther. 2017;10:178-83. doi:10.1016/j.hemonc.2017.05.007.
[2] Fuerst D, Frank S, Mueller C, Beelen DW, Schetelig J, Niederwieser D, et al. Competing-risk outcomes after hematopoietic stem cell transplantation from the perspective of time-dependent effects. Haematologica. 2018;103:1527-34. doi:10.3324/haematol.2017.183012.
[3] Liu C, Grossman BJ. Red blood cell transfusion for hematologic disorders. Hematology. 2015;(1):454-61. doi:10.1182/asheducation 2015.1.454.
[4] Cohn CS. Transfusion support issues in hematopoietic stem cell transplantation. Cancer Control. 2015;22(1):52-59. doi:10.1177/107327481502200108.
[5] Akkok Ç. Allogeneic hematopoietic stem cell transplantation: Transfusion issues. International Journal of Clinical Transfusion Medicine. 2016;4:29-42. doi:10.2147/IJCTM.S73073.
[6] Gajewski JL, Johnson VV, Sandler SG, Sayegh A, Klumpp TR. A review of transfusion practice before, during, and after hematopoietic progenitor cell transplantation. Blood. 2008;112:3036-48. doi:10.1182/blood-2007-10-118372.3036.
[7] Logan AC, Wang Z, Ali moghaddam K, Ruby wong, Tze lai, Robert S, et al. ABO mismatch is associated with increased non relapse mortality after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2015;21:746-54. doi:10.1016/ j.bbmt2014.12.
[8] Pullarkat V, Blanchard S, Tegtmeier B, Dagis A, Patane K, Ito J, et al. Iron overload affects outcome of allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2008;42:799-805. doi: 10.1038/bmt.2008.262.
[9] Brissot E, Rialland F, Cahu X, Strullu M, Corradini N, Thomas C, et al. Improvement of overall survival after allogeneic hematopoietic stem cell transplantation for children and adolescents: A three-decade experience of a single institution. Bone Marrow Transplantation. 2016;51(2):267-72. doi: 10.1038/ bmt.2015.250.
[10] Pullarkat V. Iron overload in patients undergoing hematopoietic stem cell transplant. Advances in Hematology. 2010;2010:345756. 12 pages. doi:10.1155/2010/345756.
[11] Zhang X, Xiao Y, Ran Q, Liu Y, Duan Q, Duan H, et al. Clinical observation of factors in the efficacy of blood component transfusion in patients following hematopoietic stem cell transplantation. PloS One. 2012;7(5):36912. doi:10.1371/journal.pone.0036912.
[12] Francisci D, Aversa F, Coricelli V, Carotti A, Canovari B, Falcinelli F, et al. Prevalence, incidence and clinical outcome of hepatitis B virus and hepatitis C virus hepatitis in patients undergoing allogeneic hematopoietic stem cell transplantation between 2001 and 2004. Haematologica. 2006;91(7):980-82.
[13] Slade M, Goldsmith S, Romee R, DiPersio JF, Dubberke ER, Westervelt P, et al. Epidemiology of infections following haplo identical peripheral blood hematopoietic cell transplantation. Transplant Infectious Disease. 2017;19(1):12629. doi: 10.1111/tid.12629.
[14] Lee S, Yahng S, Cho B, Eom K, Kim Y, Kim H, et al. Impact of pre-transplant red cell transfusion on outcome after allogeneic stem cell transplantation in adult patients with severe aplastic anaemia. Bone Marrow Transplantation. 2016;51:1323-29. doi:10.1038/bmt.2016.140.
[15] Hosoba S, Waller EK, Shenvi N, Graiser M, Easley KA, Al-kadhimi Z, et al. Peritransplantation red blood cell transfusion is associated with increased risk of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Biology of Blood and Marrow Transplantation. 2018;24(5):973-82. doi: 10.1016/j.bbmt.2018.01.003.
[16] Hendrickson JE, Chadwick TE, Roback JD, Hillyer CD, Zimring JC. Inflammation enhances consumption and presentation of transfused RBC antigens by dendritic cells. Blood. 2007;110:2736-43. doi:10.1182/blood-2007-03-083105.
[17] Alessandrino EP, Della Porta MG, Bacigalupo A, Malcovati L, Angelucci E, Van Lint MT, et al. Prognostic impact of pre-transplantation transfusion history and secondary iron overload in patients with myelodysplastic syndrome undergoing allogeneic stem cell transplantation: A GITMO study. Haematologica. 2010;95(3):476-84. doi: 10.3324/haematol.2009.011429.
[18] Hosoba S, Waller EK, Barclay S, Easley KA, Shenvi N, Roback J, et al. Dose and time-dependent association of red blood cell transfusion with increased risk of GVHD and worse survival after allogeneic HSCT. Blood. 2014;124:1555.

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