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ORIGINAL ARTICLE

COMPLICATIONS IN ABO-INCOMPATIBLE HEMATOPOIETIC STEM CELL TRANSPLANT IN PAKISTAN

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ABSTRACT

Background: Hematopoietic stem cell transplantation (HSCT) is therapeutic option for many blood diseases. It has increased risk of complications with incompatible pair. The objective of this study was to determine the frequency of complications in ABO-incompatible HSCT in Pakistan.

Materials & Methods: This cross-sectional study was conducted at Armed Forces Bone Marrow Transplant Centre , Rawalpindi, Pakistan from 11th August 2018 till 31st March 2021. A sample of 73 ABO-incompatible HSCT patients was selected. Variables were sex, age groups, acute & delayed hemolysis, pure red cell aplasia and acute GvHD. All variables being categorical were described by count and percentage with 80%CI. Complications in sample vs. population were compared through chi-square goodness of fit test.

RESULTS: Seventy three patients with ABO-incompatible HSCT included 52 (71.23%) men & 21 (28.77%) women, and 49 (67.12%) in age group ≤14 years & 24 (32.88%) in ≥15 years. Out of 73 patients, eight (10.96%) had acute hemolysis, 26 (35.62%) had delayed hemolysis, four (5.84%) had pure red cell aplasia and 34 (46.58%) had acute GvHD. The observed prevalence in sample was similar to population for acute (p=.46893) and delayed hemolysis (p=.30759) and acute GvHD (p=.55841), while it was different for pure red cell aplasia (p=.00006).

CONCLUSION: Most common complication in our study was acute GvHD, followed by delayed hemolysis, acute hemolysis & pure red cell aplasia. The observed prevalence in sample was similar to population for acute & delayed hemolysis and acute GvHD, while it was different for pure red cell aplasia.

KEYWORDS: Complications; Blood Group Incompatibility; Hematopoietic Stem Cell Transplantation; Population; Sex; Age Groups; Hemolysis; Pure Red Cell Aplasia; Graft Versus Host Disease; Pakistan.

1. INTRODUCTION

1.1 Background: Hematopoietic stem cell transplantation (HSCT) is treatment strategy for many hematological disorders.[1] During the preceding decades, results of HSCT have improved due to better donor selection, good supportive care, improvement in post-transplant sequelae care, and recognition of less toxic procedures. Due to these changes, HSCT indications & number of patients eligible for transplant increased globally.[2]

HSCT can be carried out in ABO blood group incompatible pair.[3] ABO incompatibility is found in 30-40% of human leukocyte antigen (HLA) matched transplants.[4] ABO-incompatible patients are divided into three different groups: major, minor and bidirectional ABO mismatch, with incidence of 15-20%, 15-20% and up to 5%, respectively.[5]

Complications like acute and delayed hemolysis, pure red cell aplasia (PRCA) and acute graft vs. host disease (GvHD) were found in ABO-incompatible HSCT affecting the outcome of transplant and required additional strategies in terms of graft manipulation and post-transplant management.[3,6-9]

Zhu, et el.[6] reported from China for the period from April 1997 to December 2006 42 ABO-incompatible HSCT cases, including 13 bone marrow transplant, 25 peripheral blood stem cell & four cord blood, and 29 grafts from related & 13 from unrelated donors.

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He reported 26.19% (11*100/42=26.19%) PRCA and 50% (21*100/42=50) acute GvHD in this sample.

Vaezi, et al.[7] from Tehran, Iran reported 486 total allogenic HSCT from 2010 to 2012, including 203 ABO-incompatible transplants, having 49.26% (100*100/203=49.26) acute GvHD ≥II.

Aung, et al. [8] from Texas for the period from January 2007 to December 2008 reported 7.45% (12*100/161=7.45) frequency of PRCA in 161 major ABO incompatible transplants out of 596 HSCT.

Tomac, et al[9] from Zagreb, Croatia from 2012 to 2013 with 36 major and bidirectional ABO-incompatible HSCT demonstrated 13.89% (5*100/36=13.89) acute hemolysis and 2.78% (1*100/36=2.78) PRCA, with no delayed hemolysis.

Worel, et al.[3] from Vienna, Austria reported 30% prevalence of delayed hemolysis in minor ABO-incompatible HSCT in a review article published in October 2015.

1.2 Research Objectives (RO 1-4): To determine the prevalence of acute & delayed hemolysis, pure red cell aplasia and acute GvHD in ABO-incompatible HSCT in Pakistan.

1.3 Research Hypotheses (Null)

H_{01}: The observed prevalence of acute hemolysis is good fitting to its expected prevalence in ABO-incompatible HSCT in Pakistan. (RO1)

H_{02}: The observed prevalence of delayed hemolysis is good fitting to its expected prevalence in ABO-incompatible HSCT in Pakistan. (RO2)

H_{03}: The observed prevalence of pure red cell aplasia is good fitting to its expected prevalence in ABO-incompatible HSCT in Pakistan. (RO3)

H_{04}: The observed prevalence of acute GvHD is good fitting to its expected prevalence in ABO-incompatible HSCT in Pakistan. (RO4)

1.4 Significance: HSCT is relatively advanced therapeutic procedure in Pakistan; that has evolved in the preceding two decades. This study will provide data regarding the magnitude of the complications in our local population. It will also create background data for future research and will help in determining future trends of the complications.

1.5 Operational Definitions

Major ABO mismatch: "When the recipient serum contains antibodies directed against donor red blood cell antigens".[5]

Minor ABO mismatch: "When the donor serum contains antibodies against recipient red blood cell antigens".[5]

Bidirectional ABO mismatch: "When both the recipient & donor sera contain antibodies directed against the donor and the recipient red blood cell antigens respectively".[5]

Acute hemolysis: "Hemolysis occurring within 7 days after ABO-incompatible HSCT".[3]

Delayed hemolysis: "Hemolysis occurring 7 days after ABO-incompatible HSCT".[3,10,11]

Pure red cell aplasia: "Pure red cell aplasia will be diagnosed when reticulocytopenia (reticulocyte count <0.5%) persists, bone marrow biopsy shows sufficient myeloid, lymphoid and megakaryocytic populations with absent erythroid precursors and the recipient is red cell transfusion-dependent more than 30 days after HSCT".[6,9]

Acute GvHD: "Classified and graded according to the Glucksberg-Seattle criteria".[12]

2. MATERIALS AND METHODS

2.1 Study Design, Settings & Duration: This cross-sectional study was conducted from 11th August 2018 till 31st March 2021 at Armed Forces Bone Marrow Transplant Center, Rawalpindi, Pakistan. It is the second of nine centres of its type in Pakistan. It caters for about 42% of bone marrow transplants from all over the country. Permission from Hospital Ethical Committee was sought prior to commencement of study. Informed consent was taken from the patients/ parents for inclusion in the study.

2.2 Population & Sampling: We assumed 100 annual ABO-incompatible HSCT cases in nine transplant centres of Pakistan. Complications like acute GvHD of 50%[6] in this population was anticipated. Online calculator Raosoft[13] gave us sample of 73 with 6% margin of error at 95%CL. Consecutive non-probability sampling method was employed. All ABO-incompatible HSCT cases were eligible.

2.3 Conduct of Procedure: Informed consent was taken from the patients/ parents before undergoing transplant. In patients less than 18 years of age consent was taken from parents. Following procedures were done before HSCT

i.   ABO blood group testing & HLA matching of donor and recipient

ii. Chemotherapy to recipient was given, where indicated

iii. Conditioning regimen was given to recipient

iv. GvHD prophylaxis to recipient was given

v.   For all major ABO-incompatible HSCTs, the stem cell product was red cell-depleted.

vi. For bidirectional ABO-incompatible HSCTs, the stem cell product was red cell- and plasma-depleted

vii. Plasma depletion was done in only one patient for minor ABO mismatch because anti-recipient antibody titer was 1:256.

viii. Antibiotics, antiviral and antifungal prophylaxis were given to recipient where indicated.

Detail history, examination and necessary inves-

tigations were done to detect complications in ABO-incompatible HSCT. Hematopoietic recovery of neutrophil and platelet were monitored after HSCT and expressed as number of days required to reach an absolute neutrophil count of 0.5×10^9/L and platelet count of 20×10^9/L without transfusion. RBC and platelet transfusion requirements were assessed by recording the day of the last RBC and platelet transfusion and total number of transfused products during HSCT. Acute GvHD was monitored till 100 days post-HSCT.

The stem cells were taken from bone marrow harvest (BMH) in 64 (87.67%) cases, from paripheral blood stem cell (PBSC) in four (5.48%) cases and from both BMH and PBSC in five (6.85%) cases. 48 (65.75%) patients received myeloablative conditioning regimen, 17 (23.29%) received non-myeloablative and eight (10.96%) received reduced intensity conditioning regimen. Processing of stem cell was done for major and bidirectional ABO mismatch. Plasma depletion was done in only one patient for minor ABO mismatch because anti-recipient antibody titer was 1:256. Mean CD34 dose was 8.4×10^6/kg $\pm$ 7.7 and mean total nucleated cell (TNC) dose was 4.9×10^8/kg $\pm$ 1.9. Neutrophil engraftment was achieved in 98.6% of patients at a median of day 13 post-transplant (range 10-20 days). One patient had primary graft failure. Platelet engraftment was achieved in 96% (n=70) of patients at a median of day 22 post-transplant. 91.8% (n=67) achieved red cell engraftment. Mean red cell concentrates transfused during the duration of transplant was 4 units $\pm$ 3.6. Regarding platelet, mean number of random donor platelet units transfused was 15 $\pm$ 16.5 and mean number of single donor platelets was 2.8 $\pm$ 2.6 units.

2.4 Data Collection Plan: Data was extracted for two demographic variables; sex (men/ women) & age group ($\leq$14 years/ $\geq$15 years.), and four research variables (acute & delayed hemolysis, PRCA & acute GvHD). All data was binary nominal.

2.5 Data Analysis Plan

2.5.1 Descriptive statistics and estimation of parameters: The variables for the sample were described by count and percentage and for population as C.I (confidence interval) for proportion at 80% C.L (confidence level) taking help of online statistical calculator.[14]

2.5.2 Testing of Hypotheses: Difference between the observed and expected prevalence of the four research variables was validated separately by chi-square goodness of fit test through an online calculator (H_{01}-H_{04}).[15-17]

3. RESULTS

3.1 Descriptive statistics & estimation of parameters

3.1.1 Sample description & prevalence of complications in ABO-incompatible HSCT: Out of 73 cases, 52 (71.23%) were men & 21 (28.77%) women, and 49 (67.12%) were in age group $\leq$14 years & 24 (32.88%) were in age group $\geq$15 years.

Out of 73 cases, eight (10.96%) had acute hemolysis, 26 (35.62%) had delayed hemolysis, four (5.84%) had pure red cell aplasia and 34 (46.58%) had acute GvHD. Estimated prevalence in population is shown below. (Table 3.1.1)

3.2 Hypotheses Testing:

3.2.1 Observed vs. expected prevalence of acute hemolysis in ABO-incompatible HSCT (H_{01}): Our observed findings of acute hemolysis (yes: no) were 8:65 (n=73) in respect to corresponding expected findings of 5:31 (n=36) by Tomac, et al[9]. With dissimilar denominators comparability was impossible. Therefore, the denominator 36 of Tomac, et al.[9] was replaced by ours denominator 73. The expected

Table 3.1.1: Prevalence of Complications in ABO-incompatible HSCT in Pakistan (n=73)

Research variables	Attributes	Sample analysis		80%CI for proportion	
		Count	%age	Lower	Upper
Presence of acute hemolysis	Yes	8	10.96	7.10	16.53
	No	65	89.04	83.47	92.89
Presence of delayed hemolysis	Yes	26	35.62	28.83	43.05
	No	47	64.38	56.95	71.17
Presence of pure red cell aplasia	Yes	4	05.48	2.94	9.98
	No	69	94.52	90.03	97.06
Presence of acute GvHD	Yes	34	46.58	39.26	54.06
	No	39	53.42	45.94	60.74
Total		73	100%	Population parameters	

counts of 5:31 (n=36) were changed to 10.14:62.86 (n=73). Adjusted expected percentages came identical to expected percentages, so not replaced. (Table 3.2.1.1)

Test of significance resulted in p-value .46893, accepting H_{01}, which proved that the observed results match the expected results of the population. Simply, the findings of 10.96% of acute hemolysis in our population is similar to the adjusted expected findings of 13.89% from Tomac, et al[9]. (Table 3.2.1.2)

3.2.2 Observed vs. expected prevalence of delayed hemolysis in ABO-incompatible HSCT (H_{02}): Our observed findings of delayed hemolysis (yes: no) were 26:47 (n=73) in respect to corresponding assumed expected counts of 22:51 from assumed sample of 73 as reported by Worel, et al.[3] from Vienna, Austria in a review article published in October 29, 2015 as 30% prevalence of delayed hemolysis in minor ABO-incompatible HSCT. As assumed denominator were similar to our denominator, so adjusted expected counts and percentages were not calculated. (Table 3.2.2.1)

Test of significance resulted in p-value .30759, accepting H_{02}, which proved that the observed results match the expected results of the population. Simply, our findings of 35.62% of delayed hemolysis is similar to the expected findings of 30.14% from Worel, et al.[3] (Table 3.2.2.2)

Table 3.2.1.1: Observed, expected and adjusted expected counts and percentages for prevalence of acute hemolysis in indoor ABO-incompatible HSCT in Pakistan (n=73)

Presence of acute hemolysis	Observed counts	Observed %ages	Expected counts	Expected %ages	Adjusted expected counts	Adjusted expected %ages
Yes	08	10.96	5	13.89	5*73/36=10.14	10.14*100/73=13.89
No	65	89.04	31	86.11	31*73/36=62.86	62.86*100/73=86.11
Total (n)	73	100%	36	100%	73	100%

Table 3.2.1.2: Observed vs. expected prevalence of acute hemolysis in ABO-incompatible HSCT in Pakistan (n=73)

Attributes	Observed count (O)	Expected count (E)	O-E	$(O-E)^2$	χ^2	p-value
Yes	08	10.14	-2.14	4.58	0.45	.46893
No	65	62.86	2.14	4.58	0.07	
Total	73	73.00	00	$\Sigma \chi^2$	0.52	d.f.=1

Table 3.2.2.1: Observed and expected counts and percentages for prevalence of delayed hemolysis in ABO-incompatible HSCT in Pakistan (n=73)

Presence of delayed hemolysis	Observed counts	Observed %ages	Expected counts	Expected %ages
Yes	26	35.62	22	30.14
No	47	64.38	51	69.86
Total (n)	73	100%	73	100%

Table 3.2.2.2: Observed vs. expected prevalence of delayed hemolysis in indoor ABO-incompatible HSCT population, Pakistan (n=73)

Variable	Attributes	Observed count (O)	Expected count (E)	O-E	$(O-E)^2$	χ^2	p-value
Presence of delayed hemolysis	Yes	26	22	4.00	16.00	0.73	.30759
	No	47	51	-4.00	16.00	0.31	
	Total	73	73	00	$\Sigma \chi^2$	1.04	d.f.=1

Table 3.2.3.1: Observed, expected and adjusted expected counts and percentages for prevalence of pure red cell aplasia in indoor ABO-incompatible HSCT in Pakistan (n=73)

Presence of pure red cell aplasia	Observed counts	Observed %ages	Expected counts	Expected %ages	Adjusted expected counts	Adjusted expected %ages
Yes	4	5.48%	11	26.19%	11*73/42=19.12	19.12*100/73= 26.19%
No	69	94.52%	31	73.81%	31*73/42=53.88	53.88*100/73=73.81%
Total (n)	73	100.00%	42	100.00%	73.00	100.00%

Table 3.2.3.2: Observed vs. expected prevalence of pure red cell aplasia in indoor ABO-incompatible HSCT in Pakistan (n=73)

Variable	Attributes	Observed count (O)	Expected count (E)	O-E	$(O-E)^2$	χ^2	p-value
Presence of pure red cell aplasia	Yes	4	19.12	-15.12	288.61	11.96	.00006
	No	69	53.88	15.12	288.61	04.24	
	Total	73	73.00	00	$\Sigma \chi^2$	16.20	d.f.=1

Table 3.2.4.1: Observed, expected and adjusted expected counts and percentages for prevalence of acute GvHD in ABO-incompatible HSCT in Pakistan (n=73)

Presence of acute GvHD	Observed counts	Observed %ages	Expected counts	Expected %ages	Adjusted expected counts	Adjusted expected %ages
Yes	34	46.58	21	50	21*73/42=36.50	36.50*100/73= 50
No	39	53.42	21	50	21*73/42=36.50	36.50*100/73=50
Total (n)	73	100%	42	100%	73.00	100%

Table 3.2.4.2: Observed vs. expected prevalence of acute GvHD in ABO-incompatible HSCT in Pakistan (n=73)

Variable	Attributes	Observed count (O)	Expected count (E)	O-E	$(O-E)^2$	χ^2	p-value
Presence of acute GvHD	Yes	34	36.50	-2.5	6.25	0.17	.55841
	No	39	36.50	2.5	6.25	0.17	
	Total	73	73.00	00	$\Sigma \chi^2$	0.34	d.f.=1

3.2.3 Observed vs. expected prevalence of pure red cell aplasia in ABO-incompatible HSCT in Pakistan (H_{03}): Our observed findings of pure red cell aplasia (yes: no) were 4:69 (n=73) in respect to expected findings of 11:31 (n=42) from Zhu, et al.[6] With dissimilar denominators comparability was impossible. Therefore, the denominator 42 of Zhu, et al.[6] were replaced by ours denominator 73. The expected counts of 11:31 were replaced by 19.12:53.88. Adjusted expected percentages came identical to expected percentages, so not changed. (Table 3.2.3.1)

Test of significance resulted in p-value < .00006, rejecting H_{01}, which proved that the observed results did not match the expected results of the population. Simply, our findings of 5.48% of pure red cell aplasia is different from the adjusted expected findings of 26.19% from Zhu, et al.[6] (Table 3.2.3.2)

3.2.4 Observed vs. expected prevalence of acute GvHD in ABO-incompatible HSCT (H_{05}): Our observed findings of acute GvHD (yes: no) was 34:39 (n=73) in respect to corresponding expected findings of 21:21 (n=42) from Zhu, et al.[6] With dissimilar denominators, comparability was impossible. Therefore, the denominator 42 of Zhu, et al.[6] were replaced by ours denominator 73. The expected counts of 21:21 were replaced by 36.50:36.50. Adjusted expected percentages came identical to expected percentages, so not changed. (Table 3.2.4.1)

Test of significance resulted in p-value .5584, accepting H_{01}, which proved that the observed results match the expected results of the population. Simply, our findings of 46.58% of acute GvHD is similar to the adjusted expected findings of 50% from Zhu, et al.[6] (Table 3.2.4.2)

4. DISCUSSION

4.1 Prevalence of acute hemolysis in ABO-incompatible HSCT (H_{01}): Our findings (n=73) disclosed 10.96% (7.10%-16.53% at 80%CL) acute hemolysis.

Tomac, et al.[9] (n=36) documented similar findings 13.89%. No data reporting different results/ findings from ours could be recovered from published studies.

Our observed findings of 10.96% acute hemolysis was similar (p=.46893) to what we expected as 13.89% from Tomac, et al.[9] (n=36).

4.2 Prevalence of delayed hemolysis in ABO-incompatible HSCT (H_{02}): Our findings (n=73) disclosed 35.62% (28.83%-43.05% at 80%CL) delayed hemolysis.

Worel, et al.[3] reported similar findings 30.14% in minor ABO-incompatible HSCT. Tomac, et al.[9] (n=36) revealed no delayed hemolysis. No data reporting higher results/ findings from ours could be recovered from published studies.

Our observed findings of 35.62% delayed hemolysis was similar (p=.30759) to what we assumed as 30.14% from Worel, et al.[3]

4.3 Prevalence of pure red cell aplasia in ABO-incompatible HSCT (H_{03}): Our findings disclosed 5.48% (2.94%-9.98% at 80%CL) pure red cell aplasia (n=73).

Aung, et al.[8] (n=161) revealed similar findings 7.45%. Lower prevalence of 2.78% than ours were reported by Tomac, et al.[9] (n=36). Higher prevalence of 26.19% than ours was reported by Zhu, et al.[6] (n=42).

Our observed findings of 5.48% PRCA (n=73) was not similar (p=.00006) to what we expected as 26.19% from Zhu, et al.[6] (n=42).

4.4 Prevalence of acute GvHD in ABO-incompatible HSCT (H_{04}): Our findings (n=73) disclosed 46.58% (39.26%-54.06% at 80%CL) acute GvHD. Similar findings were reported by Zhu, et al.[6] (n=42) 50% and Vaezi, et al.[7] (n=203) 49.26%. No data reporting different results/ findings from ours could be recovered from published studies.

Our observed findings of 46.58% acute GvHD was similar (p=.55841) to what we expected as 50% from Zhu, et al.[6] (n=42).

4.5 Marwat Logical Trajectory of Research Process: We have adapted this trajectory in this project.[18-22]

CONCLUSION

Most prevalent complication in ABO-incompatible HSCT was acute GvHD, followed by delayed hemolysis, acute hemolysis & pure red cell aplasia. The observed prevalence in sample was similar to population for acute & delayed hemolysis and acute GvHD, while it was different for pure red cell aplasia in ABO-incompatible HSCT.

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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design: MH, IU

Acquisition, Analysis or Interpretation of Data: MH, IU, NS, QUNC, MAK, TAK

Manuscript Writing & Approval: MH, IU, NS, QUNC, MAK, TAK

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.