Treatment Outcome of Haematopoietic Stem Cell Transplant in Fanconi Anaemia: Experience from a Low- and Middle-Income Country

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ABSTRACT

Objective: To determine the outcome of haematopoietic stem cell transplantation (HSCT) in Fanconi anaemia (FA) patients.

Study Design: Retrospective observational study.

Place and Duration of the Study: Department of Clinical Haematology, Armed Forces Bone Marrow Transplant Centre, CMH Rawalpindi, Pakistan, from February 2009 to December 2023.

Methodology: The data of 41 cases of FA undergoing HSCT were analysed retrospectively, from February 2009 to December 2023. Cases transformed into myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) were excluded. All cases of FA under 18 years of age having fully HLA-matched HSCT were included. A non-myeloablative conditioning regimen consisting of $Flu^{120}/Cy^{30}/ATG^{20}$ was used. Descriptive statistics were obtained for harvest source, complications, graft success, and survival.

Results: The study included 27 (65.9%) boys and 14 (34.1%) girls with a mean age of 10.3 ± 3.1 years. Bone marrow as a stem cell source was harvested in 33 (80.5%) cases. Cyclosporin-induced hypertension was documented in 36 (87.8%) cases. The cumulative incidence of acute GVHD and chronic GVHD was 34.1% and 32.3%, respectively. Six (14.6%) patients had graft failure, three had primary graft failure, and three had secondary graft failure. At a median follow-up of 63.8 ± 46.1 months, the overall survival (OS) rate was 73.2% and the disease-free survival (DFS) rate was 73.2%.

Conclusion: Overall survival of more than 70% is promising but inferior to that in developed countries. Graft failure, infectious complications, and GVHD remain major challenges requiring improvement in the developing countries.

Key Words: *Haematopoietic stem cell transplantation, Fanconi anaemia, Pakistan.*

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INTRODUCTION

Fanconi (FA) is a rare multi-organ hereditary disease characterised by bone marrow failure, congenital malformations, and predisposition to malignancies; including acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS), and epithelial cancers.[1] In 1927, Swiss paediatrician Guido Fanconi was the first person to report a family of three cases. Its incidence is around 3 per million with a carrier frequency of 1 in 300.[2] Due to a lack of published data, the prevalence of FA in Pakistan is unknown, but in one study, it was 16% in patients diagnosed with aplastic anaemia.[3]

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Currently, mutations in 23 genes designated as FANC genes have been reported to cause FA. Proteins encoded by these genes are involved in DNA damage recognition and repair, biochemical pathways. Therefore, mutant protein leads to genomic instability and chromosomal fragility.[4]

Initial reports on stem cell transplantation for FA reported high treatment response mortality (TRM) due to inherited DNA defects and chromosomal fragility.[5] Over the past 20 years, reduction in cyclophosphamide (CY) dose and irradiation-free conditioning regimens have improved the overall survival to 80-95% in developed countries.[6] The data on outcomes of haematopoietic stem cell transplantation (HSCT) for FA patients from developing countries is limited. The current study aimed to provide data on demographic patterns and transplant outcomes of FA patients undergoing HSCT.

METHODOLOGY

This study retrospectively analysed the data of the FA cases undergoing HSCT at the Armed Forces Bone Marrow Transplant Centre, CMH Rawalpindi, Pakistan, from February 2009 to December

2023. The study included all cases of FA undergoing HSCT with fully HLA-matched family donors in the aplastic phase diagnosed on bone marrow aspiration and trephine as per standard criteria. Cases transformed MDS and AML were excluded. The data of cases were extracted from the Hospital's patient records.

The Hospital's Institutional Review Board and Ethical Com-mittee approved the study. The diagnosis of FA was confirmed on the chromosomal breakage analysis. T-lymphocytes isolated from the blood sample were exposed to DNA cross-linking agent diepoxy butane (DEB) and mitomycin C (MMC), and chromosomal breakages were examined on the microscope. Bone marrow aspiration and trephine biopsy were performed in all cases to document marrow hypoplasia and to exclude MDS / leukaemia transformation. Genetic testing was performed to confirm the diagnosis after 2019, in only 3 (7.3%) cases when there was a disparity in chromosomal breakage testing and phenotypic presentation. Thorough history taking and clinical examination (Fanconi facies, short stature, skeletal anomalies or skin hypopigmentation/hyperpigmentation, renal anomalies, *etc*.) were done for all cases.

Based on the presence of FA features, cases were divided into three phenotypes: Mild, moderate, and severe. Mild phenotypes had no Fanconi features, moderate phenotypes had FA facies (microcephaly, small eyes, triangular face, epicanthal folds, and micrognathia), and severe phenotypes had FA facies and organ involvement (renal, GIT, skeletal, *etc*.).

A non-myeloablative conditioning regimen containing fludarabine (30 mg/m² once daily from day –7 to –4), anti-thymocyte globulin 5 mg/kg, once daily from day –6 to –3, and cyclophosphamide 7.5 mg/kg/day from day –5 to –2 were used in all cases.

Cyclosporine (CSA) 3 mg/kg IV twice daily was used for prophylaxis of graft-*versus*-host disease (GVHD), starting from day-2. The CSA was continued for 6-9 months and tapered over the next three months post-HSCT. The CSA levels were monitored regularly and maintained at 200 to 300 ng/ml. In the initial post- transplant phase, liver functions and kidney functions were monitored regularly.

Neutrophil engraftment was defined as the first day of three consecutive days of achieving a sustained absolute neutrophil count ANC $>0.5 \times 10^9$/L. Platelet engraftment was defined as platelet count $>20 \times 10^9$/L, independent from platelet transfusion for at least seven days.[7] Primary graft failure (PGF) was defined as the failure to achieve neutrophil engraftment by day + 28, and secondary GF as persistent neutropenia (ANC $<0.5 \times 10^9$/L) after initial engraftment.[8] Oral mucositis was graded as per WHO criteria. Veno-occlusive disease (VOD) was diagnosed and risk-stratified as per the European Society for Blood and Marrow Transplantation (EBMT) criteria. Cytomegalovirus (CMV) reactivation was labelled with CMV PCR copies of >2000/ml. Acute GVHD was diagnosed and staged according to the Glucksberg criteria.[9] while chronic GVHD as per NIH criteria.[10]

The time from the transplant date to rejection or death was defined as disease-free survival (DFS) while overall survival (OS) was defined as the time from the day of transplant to the day of the last follow-up or death.

Statistical analysis was performed with SPSS 25.0 software. Frequencies and percentages were calculated for categorical variables and mean ± SD was calculated for continuous variables. DFS and OS were compared by Kaplan-Meier survival curves using the log-rank test. Univariate and multivariate analyses for the prognostic factors with 95% confidence intervals (95% CI) were performed by the Cox proportional-hazard regression model. A p-value of <0.05 was considered statistically significant.

RESULTS

During the study period, 41 cases including 27 (65.9%) males and 14 (34.1%) females underwent HSCT. Androgens were used before going for HSCT in 25 (60%) cases and none of them showed any response to androgens. The mean time duration from the time of diagnosis to HSCT was 1.75 $\pm$ 1.79 years. At the time of HSCT, the median age was 10.3 $\pm$ 3.1 years (range 3.4 - 15.01 years). The majority of the stem cell donors had matched siblings, including 22 (53.7%) sisters and 14 (34.1%) brothers. HLA- matched mothers and fathers were donors in 3 (7.3%) and 2 (4.9%) cases, respectively. The source of stem cells was bone marrow (BM) in 33 (80.5%) cases, peripheral blood stem cell (PBSC) in 3 (7.3%), and a combination of BM and PBSC in 5 (12.2%) cases. The mean TNC dose was 5.4 ± 2.06 x 10^8/kg and the CD 34 + stem cell dose was 6.6 ± 4.2 x 10^6 /kg. Neutrophils and platelets were engrafted at a mean of 12 days and 19 days, respectively (Table I).

Table I: Demographics (n = 41).

Variables	Number	Percentage
Total number	**41**	**100**
Age at diagnosis (years)	7.51 ± 3.32	
Age at HSCT (years)	9.60 ± 3.14	
Gender		
Male	27	65.9
Female	14	34.1
ABO mismatch		
No mismatch	29	70.7
Major mismatch	7	17.1
Minor mismatch	5	12.1
Donor relation		
Brother	14	34.1
Sister	22	53.7
Father	2	4.9
Mother	3	7.3
Stem cell source		
Bone marrow (BM)	33	80.5
PBSC	3	7.3
BM + PBSC	5	12.2
FA phenotypes		
Mild	1	2.4
Moderate	21	51.2
Severe	19	46.34

Table II: Complications in FA patients (n = 41).

Parameters	Number	Percentage
Total number	41	100
Hypertension	36	87.8
Neutropenic fever	35	85.4
Mucositis	26	63.4
No mucositis	15	36.5
Grade-I	1	3.8
Grade-II	12	46.1
Grade-III	13	50
CMV Reactivation	14	34.1
Veno-occlusive disease (VOD)	1	2.4
Acute GVHD (aGVHD)	14	34.1
Grade -I	10	71.4
Grade -II	1	7.14
Grade -III	3	21.4
Chronic GVHD (cGVHD)	11	32.3
Limited Chronic Oral GVHD	7	63.6
Limited Chronic Skin GVHD	3	27.3
Chronic extensive GVHD	1	9.1
Haemorrhagic cystitis	2	4.9
CSA induced hepatotoxicity	17	41.4

Table III: Results of statistical tests of association between OS and DFS and study variables in FA (n = 41).

Variables	OS				DFS			
	Value	95% CI	Log rank	p-value	Value	95 % CI	Log rank	p-value
Age	Percentage				Percentage			
<10 years (20)	75.0	97.02 - 169.36			75.0	2981.94 - 5086.09	0.280	0.597
>10 years (21)	71.4	70.84 - 122.10	0.048	0.827	66.7	1923.89 - 3516.31		
Gender								
Male (27)	77.8	87.60 - 165.96	0.903	0.342	77.8	87.38 - 166.01	1.836	0.175
Female (14)	64.3	49.42 - 120.73			57.1	44.61 - 113.49		
Mucositis								
Yes (26)	73.1	68.48 - 111.58	0.091	0.763	73.1	69.52 - 112.08	0.032	0.857
No (15)	78.6	88.77 - 171.11			66.7	75.01 - 161.40		
CMV Reactivation								
Yes (14)	78.6%	52.24 - 90.29			78.6%	52.24 - 90.29	0.177	0.674
No (27)	70.4%	90.01 - 155.98	0.42	0.838	66.7%	84.44 - 151.00		
aGVHD								
Yes (14)	64.3%	44.44 - 102.53			57.1%	35.83 - 95.54	1.575	0.210
No (27)	77.8%	112.08 - 168.77	0.699	0.403	77.8%	112.81 - 168.9		
cGVHD								
Yes (11)	90.9%	105.82 - 111.60	2.620	0.106	90.9%	105.82 - 111.6	3.170	0.075
No (30)	66.7%	85.81 - 149.32			63.3%	81.20 - 144.56		

aGVHD: Acute graft versus host disease, cGVHD: Chronic Graft versus host disease.

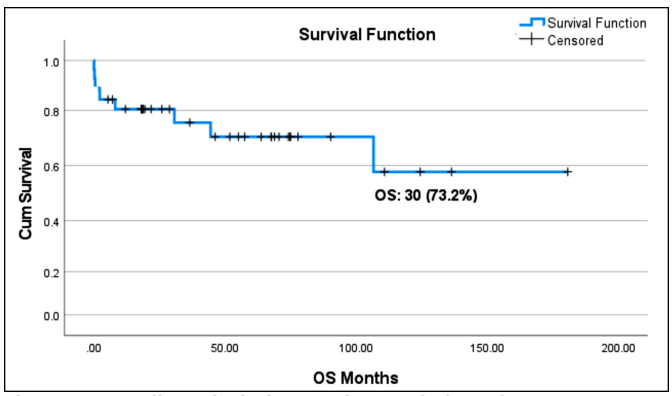

Figure 1: Overall Survival of Fanconi anaemia (n=41).

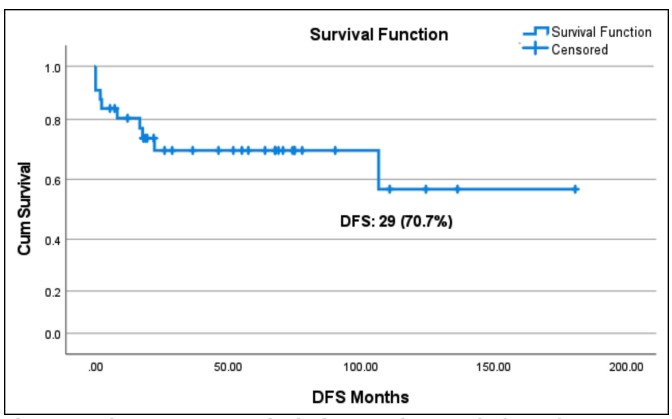

Figure 2: Disease-Free Survival of Fanconi Anaemia (n=41)

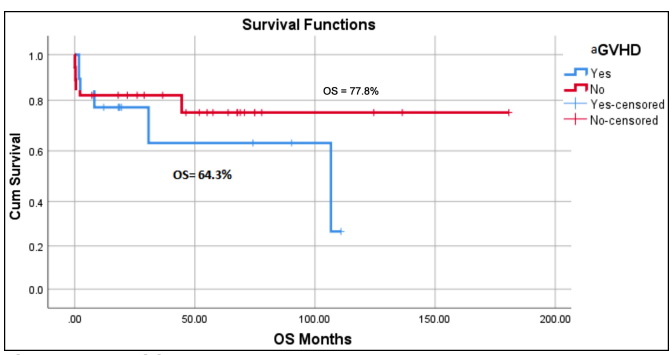

Figure 3: OS with aGVHD

The most common complication was cyclosporine-induced hypertension in 36 (87.8%) cases, followed by neutropenic fever in 35 (85.4%) cases. Mucositis was recorded in 26 (63.4%), out of which, 12 / 26 (46.1%) had grade 2, 13 (50%) had grade 3 mucositis, and only one case (4%) had grade 4 mucositis. Hepatoxicity occurred in 17 / 41 (41.5%). Two (4.9%) cases had haemorrhagic cystitis.

Acute GVHD was documented in 14 (34.1%) cases, one (7.1%) had grade II, and three cases (21.4%) had grade III GVHD. After excluding seven cases that died within 100 days, chronic GVHD was documented in 11 / 34 (32.3%) cases. Among cGVHD cases, 7 / 11 (63.6%) had limited oral GVHD, 3 (27.3%) had limited skin GVHD, and one (9.1%) case had extensive GVHD. CMV reactivation occurred in 14 (34.1%, Table II).

The total mortality of the cohort was 11 (26.8%). Out of these, 7 (63.6%) patients expired during the first 100 days of transplant, with 3 / 7 (42.8%) due to primary graft failure, 2 / 7 (28.6%) due to pulmonary haemorrhage, and 2 / 7 (28.6%) with grade III acute GVHD. Three had secondary graft rejection followed by mortality in two patients due to infection at 3.5 years in one case and transformation into AML at 3.6 years in another case. One case died of pneumonia at eight months post-transplant, and one case died of extensive chronic GVHD at eight years post- transplant.

After a median follow-up of 63.8 ± 46.1 months, the OS rate was 73.2% and the DFS rate was 73.2% and 70.07%, respectively (Figure 1 and 2). The authors also looked at various factors influencing OS and DFS. The OS was 77.8% in males and 64.3% in females (p = 0.34). OS was 77.8% in cases with no AGVHD (Figure 3) and 64.3% in cases with GVHD (p = 0.403). OS was 16.7% in cases of graft failure, while cases of no graft failure had an OS of 82.9% (p = 0.00). The patients' age, donor characteristics, mucositis, hepatoxicity, CMV reactivation, and chronic GVHD had no statistically significant impact on OS and DFS (Table III).

DISCUSSION

In the current study, the median age at the time of HSCT was 10.3 years. Similarly, Yadav *et al.* from India has reported the mean age of HSCT around nine years.[11] In FA, the conditioning regimen has evolved over the last four decades. Historically, HSCT with conditioning consisting of high-dose cyclophosphamide resulted in high mortality due to chromosomal fragility in FA.[12] FA patients had severe cyclophosphamide-induced complications, including haemorrhagic cystitis, GVHD, cardiac problems, mucositis, and intestinal bleeding. Gluckman suggested a reduction in the cyclophosphamide and irradiation dose in the conditioning regimen in the mid-80s. Since then, the conditioning regimen for HSCT in FA uses low-dose cyclophosphamide or low-dose irradiation.[12] In the 90s, fludarabine- based conditioning improved the OS in FA patients.[13] In the current study, the conditioning protocol consisted of fludarabine, low--dose cyclophosphamide, and ATG.

In the present study, the overall survival was 73%. Bonfim *et al*. from Brazil have reported an excellent outcome of around 95% in HSCT in Fanconi anaemia.[14] This lower survival rate compared to developed countries might be attributed to delayed diagnosis, possibly due to a lack of physician expertise in rare disorders, lack of diagnostic services, inadequate transfusion services, heavy transfusion burden before HSCT leading to alloimmunisation, and serious life-threatening infections. The mean TNC dose was $5.4 \pm 2.06 \times 10^8$ /Kg and the CD 34 + stem cell dose was $6.6 \pm 4.2 \times 10^6$ /kg. Fink *et al*. have reported a similar dose of CD34 around 6×10^6/kg and TNC 5.1 $x10^6$/kg.[15] The mean neutrophils and platelet engraftment were on day 12 and day 19, respectively. Doval *et al*. from India documented similar days of neutrophil and platelet engraftment at 11 and 17 days, respectively.[16]

Mucositis was documented in 26 (63.4%) cases and had no statistically significant effect on OS ($p = 0.691$) while the study by Doval *et al.* showed grade mucositis in 52% of cases.[16]

Graft-*versus*-host disease (GVHD) is a common and potentially life-threatening complication following HSCT in FA. This increased incidence of GVHD may be due to a compromised DNA repair process and increased apoptosis in target epithelial cells, leading to severe aGVHD.[17] In the present study, one-third of cases developed grade I-III acute GVHD. The aGVHD was associated with decreased OS, albeit not statistically significant, as compared to cases having no GVHD (64.3% *vs*. 77.8%, respectively, $p = 0.403$). Guardiola *et al*. showed a higher incidence of aGVHD in FA patients (62%).[18] Chronic cGVHD was documented in one-third of cases and had no statistically significant effect on OS ($p = 0.106$). Guardiola *et al*. also documented an increased incidence of aGVHD in FA cases with extensive FA phenotype (renal and urinary malformation).[18] However, the present study found no association between the FA phenotype with acute and chronic GVHD (aGVHD $p = 0.370$ and cGVHD $p = 0.657$).

One of the major challenges in FA patients after HSCT is graft failure. The European group reported 14% graft failure.[19] In the present study six (16.7%) patients had graft failure, three had primary, and three had secondary graft failure, leading to mortality in 5 (83.3%) cases and having a statistical impact on OS ($p < 0.001$). This may be due to heavy transfusion burden pre-HSCT, lack of pre-storage leucodepletion, directed blood donation, and CMV seropositivity in around 100% of cases. All these variables lead to a high risk of alloimmunisation in these patients awaiting bone marrow transplants, which is directly associated with graft failure and poor transplant outcomes.

The preferred stem cell source in severe aplastic anaemia is bone marrow for HSCT as compared to PBSC. Kumar *et al*. have reported that PBSC as a source of stem cells increased the risk of cGVHD (31% *vs*. 17%).[19] Because FA cases have an increased propensity to GVHD, stem cells collected from PBSC will enhance the chances of GVHD, especially cGVHD. Considering this, bone marrow was used as the source of stem cells in more than 80% of cases in the present study. However, cGHVD was recorded in one-third of the cases in the present study despite the use of bone marrow as a stem cell source.

Fanconi anaemia patients have a high risk of secondary malignancies following HSCT, especially solid organ cancers. A study by the European group confirmed that secondary malignancy was the main factor affecting overall survival.[20] In the present study, one case who had graft rejection was transformed into AML two years post-HSCT. This patient cohort requires long-term follow-up to accurately evaluate the long-term likelihood of developing a secondary malignancy.

The study's constraints included a limited cohort size, a lack of genetic testing and a short follow-up duration. Enhancing HSCT strategies requires a larger patient sample and prolonged follow-up. Given the rarity of FA, patient numbers are naturally limited at individual centres and require multicentre study under the umbrella of Pakistan Blood and Marrow Transplant (PBMT) society.

CONCLUSION

Haematopoietic stem cell transplantation is a curative treatment for Fanconi anaemia-related haematological abnormalities. In resource-limited settings, an overall survival rate of more than 70% is promising but inferior to that of developed countries. Graft failure, infectious complications, and GVHD remain major challenges requiring improvement in developing countries.

ETHICAL APPROVAL:

Ethical approval of the study was obtained from the Hospital's Institutional Review Board (IRB) (No: 2105/BMTC/R & P).

PATIENTS' CONSENT:

Informed consent was obtained from all patients included in the study.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

HK: Study design and analysis.
TG: Review and data curation.
TAK: Formal analysis.
NS: Data interpretation.
MNA, AS: Data collection.
All authors approved the final version of the manuscript to be published.

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