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Original Article

Fludarabine-Based Low-Intensity Conditioning for Fanconi Anemia is Associated with Good Outcomes in Aplastic Anemia but not in MDS - a Single-Center Experience

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Abstract. ***Background*: Hematopoietic stem cell transplantation (HSCT) is the only curative option for patients with Fanconi Anemia (FA) with hematological abnormalities.**
***Materials and Methods*: This is a retrospective analysis of patients with FA who underwent a matched-related donor HSCT.**
***Results*: Sixty patients underwent 65 transplants between 1999-2021 using a fludarabine-based low-intensity conditioning regimen. The median age at transplant was 11 years (range: 3-37). Aplastic anemia (AA) was the underlying diagnosis in 55 (84.6%), while 8 (12.4%) had myelodysplastic syndrome (MDS) and 2 (3%) had acute myeloid leukemia (AML). The conditioning regimen used was Fludarabine with low-dose Cyclophosphamide for aplastic anemia and Fludarabine with low-dose Busulfan for MDS/AML. Graft versus host disease (GVHD) prophylaxis consisted of Cyclosporine and methotrexate. Peripheral blood was the predominant stem cell graft source (86.2%). Engraftment occurred in all but one patient. The median time to neutrophil and platelet engraftment was 13 days (range: 9-29) & 13 days (range: 5-31), respectively. Day 28 chimerism analysis showed complete chimerism in 75.4 % and mixed chimerism in 18.5%. Secondary graft failure was encountered in 7.7%. Grade II–IV acute GVHD occurred in 29.2%, while Grade III-IV acute GVHD occurred in 9.2%. Chronic GVHD was seen in 58.5% and was limited in most patients. The median follow-up is 55 months (range: 2-144) & the 5-year estimated overall survival (OS) is 80.2 ± 5.1%. Secondary malignancies were noted in 4 patients. The 5-year OS was significantly higher in patients undergoing HSCT for AA (86.6 ± 4.7%) as compared to MDS/AML (45.7±16.6%) (p= 0.001).**
***Conclusion*: SCT using a fully matched donor provides good outcomes with low-intensity conditioning regimens in patients with FA who have aplastic marrow.**

Keywords: Fanconi anemia; Fludarabine; Low-dose cyclophosphamide; Low-dose busulfan; Graft versus host disease; Secondary malignancies.

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Introduction. Fanconi Anemia (FA) is the most common inherited bone marrow failure syndrome classically characterized by somatic malformations, progressive bone marrow failure, and predilection to both hematological and solid organ malignancies.[1,2] The incidence of the latter increases with exposure to alkylating and DNA cross-linking agents.[3,4] Despite advances in the therapeutic strategies to manage FA and its myriad manifestations, allogeneic hematopoietic stem cell transplantation (HSCT) remains the only therapy that corrects the hematological manifestation of FA.[5] HSCT for FA was attempted as early as the 1980s, with the initial transplants employing a preparatory regimen combining high doses of Cyclophosphamide (200mg/kg) and Total Body Irradiation (TBI) similar to the regimens used for acquired aplastic anemia.[4,6] Outcomes were poor, with high morbidity and mortality - mainly related to regimen-related toxicity (RRT) and graft versus host disease, coupled with an increased predisposition to late post-transplant malignancies.[6] This outcome was attributed to the hypersensitivity of FA cells to high doses of radiation and Cyclophosphamide.[7,8] In the next decade, a reduction in the doses of Cyclophosphamide and Total Body Irradiation (TBI) was realized to reduce treatment-related mortality, but that resulted in poor engraftment and graft function.[9–11] Fludarabine, an antimetabolite with potent immunosuppressive action, was incorporated into the conditioning regimens in the mid-'90s. Fludarabine, not associated with DNA cross-linking, substantially reduced the incidence of GVHD/ RRT in patients with FA.[12] We have previously described a small series of patients who underwent transplants using a combination of Fludarabine and low-dose Cyclophosphamide with promising outcomes.[12] We describe a larger experience using a fludarabine-based preparatory regimen for HSCT in patients with FA.

Materials and Methods. This study is a retrospective analysis of patients with FA who underwent a matched-related donor HSCT in the Department of Haematology, Christian Medical College Vellore, between 1990 and 2021. It was approved by the local institutional Ethics committee.

Patients and donors. The diagnosis of FA was confirmed using chromosomal breakage analysis (CBA) studies with mitomycin C. In patients with equivocal results on CBA, the diagnosis was confirmed either by analysis of the ubiquitination status of FANC- D2 on peripheral blood or skin fibroblasts or by mutation analysis. Western Blot has been available for use since 2015 at our centre. This study included only patients who received stem cells from a matched related (sibling/ non-sibling) donor; alternative stem-cell donor transplants were excluded. All donors were screened and confirmed to be negative by chromosomal breakage analysis studies.

Conditioning Regimen and GVHD prophylaxis. The choice of conditioning regimen was based on the type of hematopoietic failure - aplastic anemia (AA) or myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML) at HSCT.

Patients with AA received a combination of Fludarabine (30 mg/m^2/day x 6 days) and a low dose of Cyclophosphamide (10 mg/kg/day x 2 days). Four patients initially received low-dose ATG (ATGAM 10 mg/kg/day x 4 days), but since 2016, ATG was omitted from the preparative regimen. Patients with MDS/AML received Fludarabine (30 mg/m^2/day x 6 days) and intravenous low-dose Busulfan (2.4 mg/kg/day IV x 2 days). The dose of Busulfan was adjusted after the first dose to target a total AUC of 5000 – 6000 ng/ml.

Graft versus Host Disease (GVHD) prophylaxis consisted of Cyclosporine and a short course of methotrexate for all patients.

Transplant outcomes. The primary endpoint of the analysis was overall survival at 5 years. Neutrophil and platelet engraftment was defined as per standard CIBMTR criteria. Whole blood chimerism using short tandem repeats was assessed on Day 28, day 60, day 100, and at one year. Primary graft failure was defined as failure to achieve an (ANC >500/mm^3) by day +28, while secondary graft failure was defined as evidence of initial engraftment (ANC >500/mm^3), followed by subsequent fall in counts (ANC<500/mm^3) for 7 continuous days. Secondary endpoints included engraftment, regimen-related toxicity, and cumulative incidence of acute and chronic GVHD, which were defined and graded by standard Glucksberg criteria.[11] Patients were screened for the development of secondary malignancies at each follow-up visit.

Statistical Analysis. Statistical analyses were performed using IBM SPSS software - version 24. Continuous variables were summarized as medians, range, and categorical variables as percentages. Overall survival was estimated using the Kaplan-Meier estimators and Cox regression analysis, and comparisons between groups were conducted with a chi-square test or a Fisher's exact test (2-sided) wherever appropriate. $P <$ 0 .05 was considered significant.

Results.

Baseline characteristics. Between 1990 and December 2021, 60 patients with FA underwent 65 transplants using a fully matched related donor. Baseline characteristics are described in **Table 1**. The median age was 27 months (3-156) at diagnosis and 11 years (3-37) at HSCT. Indications for HSCT included: AA in 55 transplants (84.6%), MDS in 8 (12.4%), and AML in 2 (3%). Prior to HSCT, most (89.2%) had failed treatment with androgens (oxymetholone/stanozolol/danazol). The

Table 1. Demographic and clinical characteristics of patients at baseline.

Baseline Patient Characteristics	N% / Median (Range)
Age at diagnosis (Months)	27 (3-156)
Age at transplant (Years)	11 (3-37)
Gender	
Male	42 (70%)
Female	18 (30 %)
Hematological presentation	
Aplastic Anemia	55 (84.6%)
Myelodysplastic Syndrome	8 (12.4%)
Acute Myeloid Leukemia	2 (3%)
No. of Transfusions prior to SCT	15 (1-150)
Donor	
Matched Sibling Donor	46 (70.8 %)
Matched family Donor	19 (29.2 %)
Stem cell Source	
Bone Marrow	9 (13.8 %)
PBSC	56 (86.2 %)
Stem cell dose (CD 34^+ cells x 10^6/ kg)	10 (2.2 - 36.3)
Donor/ recipient Sex	
Male/ Female	9 (13.9%)
Male/ Male	19 (29.2%)
Female/ Male	26 (40%)
Female/ Female	11 (16.9%)
Conditioning Regimen	
Fludarabine-Cyclophosphamide	53 (81.6%)
Fludarabine-Busulfan	7(10.8%)
Others†	5 (7.6%)
GVHD Prophylaxis	
Cyclosporine-Methotrexate	56 (86.3%)
Cyclosporine	6 (9.2%)
Cyclosporine- MMF	2 (3%)
Tacrolimus- Methotrexate	1 (1.5 %)

†Others - Fludarabine with Cyclophosphamide with TBI (1); Daunorubicin- cytarabine (7+3 Induction for AML; No specific preparatory regimen) (1) and Etoposide - Cyclophosphamide-Cytarabine (1) – Cyclophosphamide with low dose TBI (1).

median number of transfusions received prior to HSCT was 15 (range 1-150).

Transplant. Sixty transplants were done upfront, 3 patients underwent a second transplant for rejection, and 1 required two transplants because of disease relapse. The stem cell source included G-CSF-stimulated peripheral blood stem cells (PBSC) in 56 and unmanipulated bone marrow (BM) in 9. The median cell dose infused was 10×10^6 CD 34 cells/kg (range: 2.2–36.3). For all second transplants, PBSC was the graft source used.

Engraftment and Chimerism. Engraftment occurred in all (98.4%) except one who expired less than two weeks after SCT due to gram-negative septicemia. The median time for neutrophil engraftment was 13 days (9–29), and also for platelet engraftment with a range of 5-31. Day 28 chimerism was complete donor chimerism in 50 (76.9%) transplants, of which 43 (66.1%) maintained complete donor chimerism on follow-up. Mixed donor-recipient chimerism was noted in 12 (18.5%) on day 28. All patients with mixed chimerism had aplastic anemia at the time of HSCT. Seven patients with complete donor chimerism on day 28 were noted to have mixed chimerism on follow-up. As per institutional protocol, a reduction of immunosuppression was attempted in 19 transplants with mixed chimerism, and 13 (68.4%) attained complete donor chimerism during subsequent follow-up. One patient required donor lymphocyte infusion to attain complete donor chimerism. Secondary graft failure was noted in 5 (7.7%) patients, of which 3 had initially achieved complete donor chimerism on day 28. A second stem cell transplant with reduced-intensity conditioning was offered to the patients with SGF, of which 3 opted for the same. Only one patient attained engraftment and complete chimerism on Day 28 following the second transplant.

Regimen Related toxicity (RRT) and GVHD. Grade 3-4 mucositis was seen in 11 (16.9%) transplants (**Table 2**). Liver dysfunction (transient elevation of liver enzymes and hyperbilirubinemia) was noted in 6 (9.2%), while veno-occlusive disease was diagnosed in 3 (4.5%), and hemorrhagic pancreatitis was noted in 2 (3.4%). There were no deaths related to RRT. There was no significant difference in the incidence of mucositis ($p = 0.35$) or veno-occlusive disease ($p = 1.0$) between patients having AA or AML/MDS at the time of HSCT.

The Day 100 cumulative incidence of acute graft versus host disease (GvHD) was 29.2%, while grade III-IV GVHD was 9.2%. Chronic GVHD was noted in 38 patients (58.5%) on follow-up; this was limited in 23

Table 2. Complications following allogenic Stem Cell Transplant.

Regimen Related Toxicity	
Mucositis (grade III/ grade IV)	11 (16.9%)
Veno-Occlusive Disease	3 (4.6%)
Calcineurin Induced TMA	3 (4.6%)
Liver Dysfunction†	6 (9.2%)
Others‡	5 (7.7%)
Day 28 chimerism§	
Complete	50 (76.9%)
Mixed	12 (18.5%)
Graft failure	
Primary graft failure	1 (1.5%)
Secondary Graft Failure	5 (7.7%)
GVHD	
Acute GVHD grade II – IV	19 (29.2%)
Acute GVHD grade III-IV	6 (9.2%)
Chronic GVHD	38 (58.5%)

†Includes patients who had transaminitis ± hyperbilirubinemia not qualifying the definition of Veno-Occlusive Disease.
‡ Others include cyclophosphamide-induced Hemorrhagic Cystitis (n=1); Cyclophosphamide induced heart failure (n=2); Hemorrhagic pancreatitis (n=2).
§ Day 28 chimerism – could not be assessed in 3 patients-2 patients expired before completion of 28 days of transplantation, 1 patient had primary graft failure.

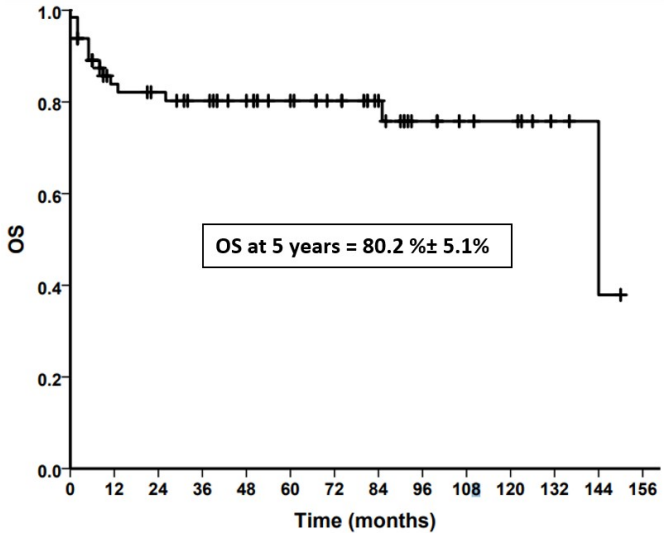

Figure 1 shows the overall survival at 5 years.

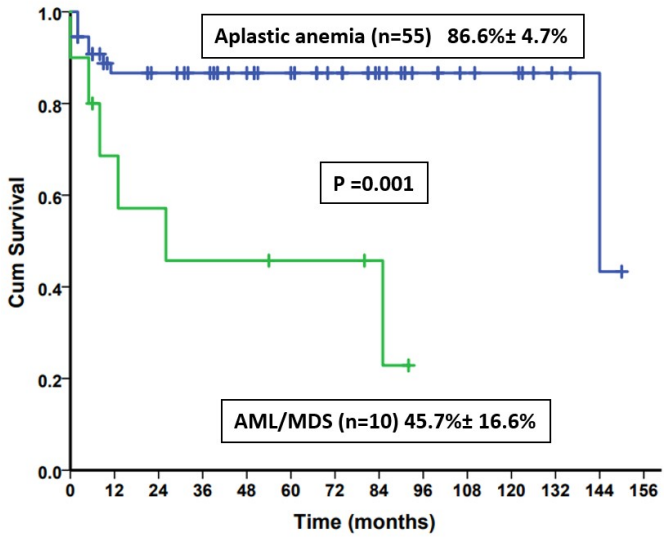

Figure 2 shows the overall survival at 5 years post HSCT in FA patients with aplastic anemia or MDS/AML.

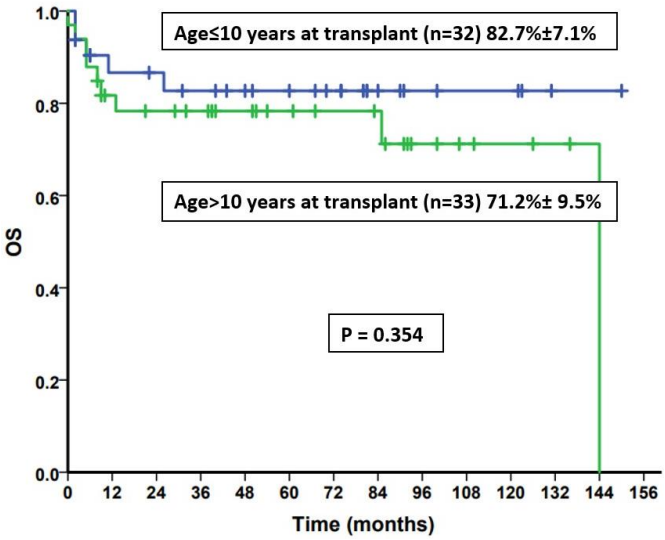

Figure 3 shows no difference in overall survival at 5 years post HSCT in FA patients irrespective of age at transplant.

(35.9%) and extensive in 15 transplants (22.6%).

Infections. Febrile neutropenia occurred in all transplants though bacteremia was documented in only 13 (20%), and it was mainly gram-negative infections more than gram-positive (69.2% vs. 30.7%). Viral reactivation (Cytomegalovirus) necessitating therapy was seen in 19 (29.2%) patients, of which ten patients had underlying grade III/IV GVHD and were on systemic corticosteroids. Six patients (9.2%) developed possible invasive fungal disease (IFD) based on imaging.

Secondary Malignancies. Of the 60 patients who underwent HSCT, 4 (6.7%) patients developed second malignancies – mainly squamous cell carcinoma of the head and neck on follow-up at a median of 8 years post HSCT (range: 6-13 years). They were treated with surgery ± radiotherapy. Two patients attained remission and are on follow-up, while the other two succumbed to the malignancy. One patient with aplastic anemia transformed into acute myeloid leukemia post-SCT. Amongst the cohort of patients undergoing SCT for MDS/AML, four patients had a relapse/ progression to AML on follow-up.

Survival Outcomes. Forty-six patients are alive at a median follow-up of 55 months (2-144 months). The 5-year overall survival in our cohort is 80.2% ± 5.1% (**Figure 1**). Six patients died due to infective complications, five expired due to secondary malignancies/ relapse of acute myeloid leukemia, two due to graft failure, and one due to extensive chronic GVHD.

The presence of MDS/AML at the time of HSCT was the only factor noted to have independently influenced survival (**Table 3**). The 5-year OS was significantly lower in patients who underwent transplants for MDS/AML (45.7 $\pm$ 16.6%) compared to aplastic anemia (86.6 $\pm$ 4.7%) (p= 0.001) (**Figure 2**). The choice of conditioning regimen did not impact survival, though the univariate analysis demonstrated better survival in patients who received Fludarabine - Cyclophosphamide. This improvement was attributed to the choice of conditioning regimen being closely linked to the underlying hematological disorder. Age at the time of HSCT also did not influence the 5-year OS in our study (p=0.35) (**Figure 3**).

Discussion. The advent of Fludarabine-based reduced-intensity conditioning regimens has led to a massive reduction in treatment-related mortality and long-term complications of HSCT, i.e., the incidence of secondary malignancies and chronic GVHD, thus leading to better long-term survival. There is limited data available on the outcomes of allogeneic SCT from resource-limited settings, and we report our experience in allogeneic stem

Table 3. Predictors of Overall Survival.

Characteristic	Univariate Analysis (Cox regression Hazards Ratio with 95% Confidence interval and p-value)		
	HR	95% CI	p-value
Age at transplant (<10 years vs >10 years)	1.663	0.56-4.97	0.362
Sex	0.667	0.21-2.04	0.479
Diagnosis at Transplant Aplastic Anemia vs MDS/AML	5.502	1.84-16.41	0.002
Type of Donor Sibling vs Non sibling donor	2.116	0.72-6.20	0.171
Stem cell source Bone marrow vs PBSC	1.026	0.2-4.9	0.975
Conditioning Regimen Flu-Cy vs Others†	4.581	1.54-13.64	0.006
Secondary Graft Failure	3.568	0.75-16.77	0.107
Acute GVHD	1.624	0.55-4.84	0.384
Chronic GVHD	2.494	0.69-8.97	0.162

†Others – Fludarabine- Busulfan, Cyclophosphamide- TBI, Fludarabine with Cyclophosphamide with TBI; Daunorubicin- cytarabine (7+3 Induction for AML; No specific preparatory regimen) and Etoposide - Cyclophosphamide- Cytarabine.

cell transplants for patients with FA.

We observed a 5-year-overall survival of 80% in our study population, which was comparable to the multicenter study conducted by Latour et al. (76%), Ayas et al. (85%), Smetsers et al. (76%) and Farzin et al. (89%).[10,13–15] All patients received fludarabine-based preparatory regimens, with no mortality related to regimen-related toxicity or primary graft failure. Data from the Chinese Bone Marrow Registry (CBMTR) suggested that OS and EFS were both 100% with the use of Fludarabine and Cyclophosphamide in patients with FA.[16]

Although the overall survival of SCT for aplastic anemia in FA shows promising outcomes, the results were not similar for FA patients with MDS/AML. The cohort of patients with MDS/AML had significantly lower overall survival (46%), corroborating previous data suggesting that clonal evolution at HSCT was a major predictor of the outcome.[13,15,17,18] This datum is similar to that from the CIBMTR, where in a study of 113 patients with FA, the outcome of patients with MDS/acute leukemia was 43%.[19]

Though the rates of acute GVHD (grade III-IV) were low (9.2%), we experienced a higher incidence of chronic GVHD (58.5%) when compared to the EBMT group (acute GVHD 19%; chronic GVHD 20%).[13] This may be related to the higher use of peripheral blood stem cells (86.2%) in our cohort in comparison to other studies that used predominantly bone marrow harvested stem cells (Latour et al. (66%) and Farzin et al. (91%)).[13,14] Although peripherally derived stem cells are known to be associated with a greater risk of chronic GVHD, we have used them in our patients, per our experience with PBSC grafts in acquired aplastic anemia. Engraftment and immune reconstitution are hastened with the use of PBSC grafts, which reduce the incidence of severe sepsis and, thereby, mortality in our setting. However, we are considering using Bone Marrow as the graft source, given the higher incidence of chronic GVHD.

Secondary graft failure was documented in 9.1% of the transplants, which again was similar to that published by the EBMT group (6%).[13] The primary cause of mortality in our study was infectious complications.

Age at transplant has been identified as one of the main variables influencing an SCT's overall outcome. When transplanted in the first decade of life, FA patients have been shown to have consistently better outcomes in various studies.[6,13] In our cohort, we did not find such a difference with age, which may reflect better tolerance of patients to reduced intensity fludarabine-based conditioning regimens.

The distinct genomic instability of FA leads to an increased propensity towards secondary malignancies.[8,20,21] The hazard is 2%/y at age 24, 4%/y at age 30, and close to 8%/y at age 40.[7,20] In addition, SCT has been postulated to increase further the risk of secondary malignancies in patients with FA.[7,22,23] The German Fanconi Anemia Registry demonstrated that patients undergoing SCT had a 3.8-fold higher risk of developing solid organ malignancies than those who did not receive an SCT.[22] However, the incidence of secondary malignancies in our cohort was 6.7%, corresponding to the risk portended by the disease per se. This value was per the findings of Rosenberg et al. but contradicted what was observed in the EBMT group (15%).[7,13] Using non-irradiation-based conditioning regimens and better modalities for limiting and treating chronic GVHD has probably influenced this moderation in the incidence of solid organ malignancies.

This study describes a large cohort of patients with Fanconi anemia that have undergone HSCT in India. The major drawbacks of this study are the retrospective

nature of data and the heterogeneity of the patients enrolled in it. Genetic studies defining the underlying FA mutations were unavailable for all the enrolled patients. Hence, identifying subsets of patients with a propensity toward high-risk disease and the probability of higher regimen-related toxicity was not feasible. However, the rarity of the disease limits more extensive prospective trials for FA.

To summarize, HSCT remains the principal treatment option to correct the hematological manifestations of FA. Given the high incidence of GVHD, it may be preferable to use bone marrow grafts, especially in children. Though the overall survival rates are on the rise, long-term morbidity in the form of chronic GVHD and secondary malignancies remains a formidable setback to a successful HSCT, requiring further modifications in the approach to SCT in FA.

Author Contributions. George B and Chattopadhyay S conceptualized the study, provided data, analyzed the data, and wrote the manuscript. Lionel S, Selvarajan S, Devasia AJ, Korula A, Kulkarni U, Aboobacker FN, Sindhuvi E, Srivastava A, Abraham A, and Mathews V contributed patient data to the study. Lakshmi KM analyzed the data and provided statistical support. All authors were responsible for the critical review and revision of the manuscript.

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