Favorable Outcomes after Haploidentical CD34-Enriched Stem Cell Transplantation for Fanconi Anemia

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Background / Objective

Fanconi anemia (FA) is an inherited DNA repair disorder characterized by congenital anomalies, progressive bone marrow failure, clonal evolution, and increased malignancy risk. Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only established curative therapy for FA-associated marrow failure; however, donor availability, graft failure, graft-versus-host disease (GVHD), and regimen-related toxicity remain major barriers. We report favorable outcomes using a radiation-free, reduced-intensity haploidentical HSCT platform incorporating rabbit anti-thymocyte globulin, ex vivo graft manipulation/T-cell depletion, CD34+ stem cell enrichment, and calcineurin inhibitor-based GVHD prophylaxis.

Methods

We performed a retrospective case series of two pediatric patients with FA-associated marrow failure who underwent haploidentical peripheral blood stem cell transplantation at Phoenix Children's Hospital. FA was confirmed by chromosome breakage testing and/or molecular testing. Transplant variables, graft characteristics, engraftment, donor chimerism, GVHD, complications, transfusion independence, and survival outcomes were reviewed.

Key Results

2 pediatric FA patients underwent haploidentical PBSC transplantation at Phoenix Children's Hospital.

Radiation-free reduced-intensity Bu/Flu/Cy + rATG conditioning was used in both cases.

Grafts were T-cell depleted and CD34 selected; one patient also received controlled CD3 add-back.

Both patients achieved durable hematopoietic recovery and transfusion independence.

Neither patient had active acute or chronic GVHD at latest follow-up.

Both patients alive and transfusion independent at 3.2 and 2.3 years post-HSCT.

Case 1 Highlights

7-year-old boy
FA confirmed by DEB/MMC chromosome breakage; abnormal telomere testing
Donor: mother, 9/12 haploidentical
Graft: PBSC, T-cell depleted, CD34 selected
CD34+ dose: 11.7 × 10^6/kg
Conditioning: Bu/Flu/Cy + rATG; no TBI
Cyclosporine prophylaxis
Neutrophil engraftment: day +16
Platelet engraftment: day +33
Chimerism: 93% donor T cells by year 2 after early mixed T-cell chimerism
Complications: adenovirus, BK viruria
Latest outcome: alive, transfusion independent, no active GVHD, Lansky 100, 3.2 years

Case 2 Highlights

9-year-old boy
FA confirmed by chromosome breakage; pathogenic FANCA variant
Donor: father, 5/10 haploidentical
Graft: PBSC, T-cell depleted, CD34 selected, CD3 add-back
CD34+ dose: 6.62 × 10^6/kg; CD3+ dose: 5 × 10^5/kg
Conditioning: Bu/Flu/Cy + rATG; no TBI
Cyclosporine prophylaxis
Neutrophil engraftment: day +12
Platelet outcome: delayed immune-mediated thrombocytopenia; ultimately recovered
Chimerism: sustained 100% donor chimerism
Complications: recurrent AIHA, EBV, norovirus, bacterial infections, hypogammaglobulinemia, TMA
Latest outcome: alive, transfusion independent, no active GVHD, Lansky 80, 2.3 years

Figure 1. Haploidentical CD34-selected transplant platform and outcomes

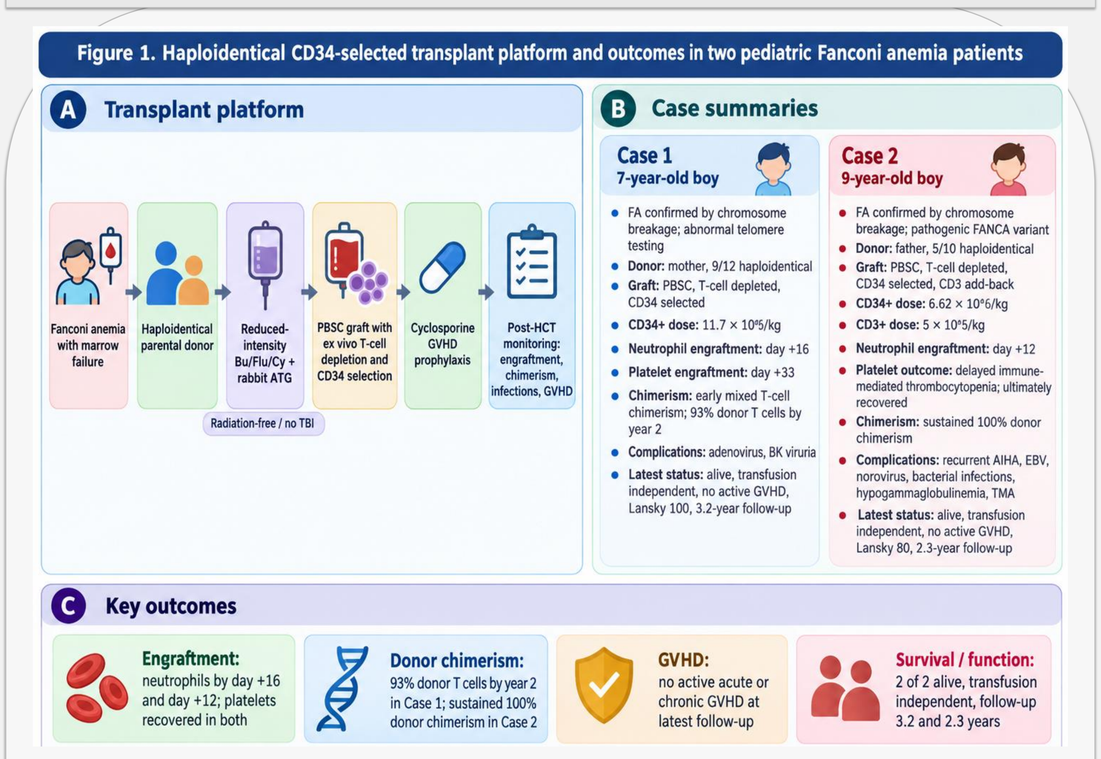

Figure summary: Both children underwent radiation-free reduced-intensity haploidentical PBSC transplantation with ex vivo T-cell depletion and CD34 selection. The figure highlights prompt neutrophil engraftment, durable donor chimerism, low active GVHD burden, and survival with transfusion independence.

Results

Both patients were male and underwent haploidentical HSCT at approximately 7 and 9 years of age. Case 1 had chromosome breakage-confirmed FA with 64% abnormal cells after diepoxybutane exposure and 56% abnormal cells after mitomycin C exposure, as well as markedly abnormal telomere testing. Case 2 had chromosome breakage-confirmed FA with a pathogenic FANCA variant and a notable family history of FA-associated AML in a sibling. Donors were haploidentical parental donors: maternal 9/12 matched donor for Case 1 and paternal 5/10 matched donor for Case 2. Both patients received reduced-intensity busulfan/fludarabine/cyclophosphamide-based conditioning without total body irradiation.

Graft manipulation included T-cell depletion and CD34+ selection; infused CD34+ cell doses were 11.7 × 10^6/kg and 6.62 × 10^6/kg, respectively. GVHD prophylaxis included rabbit ATG and cyclosporine. Neutrophil/WBC engraftment occurred by day +16 and day +12, respectively. Platelet engraftment occurred by day +33 in Case 1; Case 2 had later immune-mediated cytopenias but ultimately achieved transfusion independence. Case 1 experienced early mixed T-cell chimerism that improved after cyclosporine discontinuation, reaching 93% donor T-cell chimerism by year 2. Case 2 maintained sustained 100% donor chimerism. At most recent follow-up, both patients were alive and transfusion independent at approximately 3.2 and 2.3 years post-HSCT, respectively. Neither patient had active acute or chronic GVHD at latest assessment.

Clinical Applicability

This two-patient experience supports haploidentical HSCT using graft manipulation, CD34+ enrichment, rabbit ATG serotherapy, and cyclosporine-based prophylaxis as a feasible alternative donor strategy for FA patients lacking matched donors. Early referral and transplantation before clonal evolution may be particularly important in genetically high-risk FA families.

Conclusion

Haploidentical CD34-enriched HSCT with reduced-intensity, radiation-free conditioning achieved durable hematopoietic recovery, transfusion independence, and low active GVHD burden in pediatric FA patients.