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Improving survival for Fanconi anemia patients

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In this issue of Blood, MacMillan et al give the results of sequential modifications of the conditioning regimen to improve the outcome of unrelated bone marrow transplantation in Fanconi anemia (FA). Over a period of 10 years, they show that transplant toxicity has decreased and engraftment has improved, resulting in a 5-year overall survival probability of 94%. The major change was the use of fludarabine in the conditioning, with decreased doses of irradiation and cyclophosphamide. They attribute their success to progressive modifications of the conditioning regimen; nevertheless, the improvement may also have been due to better patient selection, use of high-resolution HLA typing for donor selection, and improved supportive care treatment.

FA is a rare genetic disease characterized by progressive bone marrow failure, malformations, and a high propensity of malignancies, including acute myeloid leukemia/myelodysplastic syndrome and squamous cell carcinomas. FA is caused by biallelic mutations in 1 of the 17 gene mutations (called FA complementation groups A through Q) involved in DNA repair processes known as the FA pathway. The underlying cause is genomic instability resulting from the deficiency in the replication-dependent DNA cross-link repair pathway commonly referred to as the FA/BRC A pathway. The prognosis of FA patients is poor, most dying before the age of 10 years from severe aplastic anemia. The only known curative treatment is hematopoietic stem cell transplant. Historically, it was recognized that the combination of alkylating agents and irradiation previously used for conditioning for acquired aplastic anemia led to unacceptable toxicity in FA patients. In vitro testing of FA cells with an alkylating agent such as cyclophosphamide, diepoxybutane, or mitomycin C showed increased chromosome breaks, which became the basis for FA diagnosis. Following this observation, the conditioning protocol was modified by reducing the doses of cyclophosphamide and irradiation, resulting in a dramatic improvement in survival. Several complications remained, including increased incidence and severity of acute and chronic graft-versus-host disease and, long-term, a high incidence of head and neck carcinomas. Because of these short- and long-term complications, the use of matched unrelated donors led to higher mortality compared with HLA-identical sibling transplants. Unfortunately, there is still a high proportion of patients who do not have a suitable HLA-matched related or unrelated bone marrow donor. HLA-mismatched transplants are currently being investigated. Unrelated HLA-mismatched cord blood transplant has proved its efficacy to treat a high number of patients with malignant or nonmalignant hematologic disorders. A preliminary analysis published in 2007 in patients with FA showed disappointing results, with an overall survival rate of 40%. Since that publication in 2007, donor selection has been changed. Now, it is recommended to select units with low-resolution HLA-matched (6/6) or only 1 antigen mismatched (5/6) and 5 × 10^6 total nucleated cells per kilogram of cord blood for transplant in nonmalignant diseases. Further, new methods of ex vivo expansion of cord blood CD34 cells have dramatically increased the engraftment probability. More recently, results of related HLA-haploidentical T cell–depleted transplant have been reported in a single-center study, with a 5-year survival rate of 83%. Despite this encouraging result of haplotransplant, long-term follow-up and well-designed prospective studies are needed. With increasing experience over the years, results of hematopoietic stem cell transplant have improved for FA patients. The major challenge is the prevention of late complications, including head and neck carcinoma.

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REFERENCES

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