Haploidentical Donor Bone Marrow Transplantation for Severe Aplastic Anemia

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KEYWORDS

- Severe aplastic anemia • Cyclophosphamide • Haploidentical transplant
- Graft versus host disease

KEY POINTS

- Relapsed and refractory SAA carries a grave prognosis if efforts to renew hematopoiesis and avoid clonal evolution are not pursued.
- Allogeneic bone marrow transplantation addresses the acute and chronic complications of SAA, by virtually eliminating the risk of relapse and secondary clonal disease but introduces the risk of acute and chronic GVHD.
- High-dose cyclophosphamide (50 mg/kg/d × 4 days) has a unique history in the context of AA for transplant and nontransplant therapies.
- Use of post-transplantation cyclophosphamide on Days 3 and 4 post-transplant has allowed for expansion of the donor pool to include haploidentical transplants for patient with relapsed and refractory SAA.
- Rates of GVHD and other transplant-related mortality are low with use of post-transplantation cyclophosphamide.

INTRODUCTION

Acquired severe aplastic anemia (SAA) is an immune-mediated hematopoietic stem cell disorder that presents with a hypocellular marrow and pancytopenia.[1,2] The incidence is roughly 1 in 250,000 individuals per year.[3,4] Most newly diagnosed patients are managed with immunosuppressive therapy (IST) unless they are young and have a suitable human leukocyte antigen (HLA)-matched sibling donor for bone marrow

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transplantation (BMT). IST improves hematopoiesis and decreases the early mortality of the disease. SAA is not considered overtly malignant, but clonal hematopoiesis is present in more than 60% of patients at diagnosis; commonly mutated genes include *PIGA*, *BCOR/BCORL1*, *DNMT3A*, and *ASXL1* among others.[5–7] This explains the high rate of paroxysmal nocturnal hemoglobinuria (PNH) and myelodysplastic syndromes (MDS) that frequently arise from SAA 5 years or more after treatment with IST.[8–11] Infection (usually fungal) is the most common cause of early death in patients with SAA; however, hemorrhage, clonal disease (MDS,[12] leukemia, PNH), and transfusional iron overload are other causes of severe morbidity and mortality.[13] Improved supportive care has led to significant progress in controlling the acute aspects of the disease (bleeding and infection), but little progress has been made controlling the late complications of SAA, especially the risk for relapse and secondary clonal disorders following IST. Indeed, SAA that is refractory or relapses after antithymocyte globulin (ATG)/cyclosporine is associated with a high degree of morbidity and mortality. Curative strategies are desperately needed for these patients.

Allogeneic BMT addresses the acute and chronic complications of SAA by virtually eliminating the risk of relapse and secondary clonal disease, but introduces the risk of acute and chronic graft-versus-host disease (GVHD). Thus, allogeneic BMT from an HLA-matched sibling donor is the standard of care for young, newly diagnosed patients with SAA,[2,14] with long-term survival rates approaching 90% in patients younger than 20 years[15,16] and 76% for patients older than 20 years.[16] The less favorable transplant outcomes in older (>30–40 years) patients is attributed to reduced engraftment, and higher rates of GVHD.[17]

When to apply alternative donor BMT has remained an active research question for many years. More recently, there has been an increase in HLA haploidentical BMT (haplo-BMT) from family members globally[18–20] for all diseases. For SAA in particular, a European survey showed that haploidentical donors constituted 6.7%, whereas cord blood is used in 3.2% of transplants in AA.[18] This is only likely to increase as outcomes improve with haploidentical transplant for SAA. Here, we review the outcomes in relapsed and refractory disease and upfront use of haplo-BMT for patients suffering with SAA.

HAPLOIDENTICAL TRANSPLANT STRATEGIES

The ideal BMT regimen in AA is one that results in sustained engraftment, minimal toxicity from the regimen, lack of acute or chronic GVHD, and allows most patients (old and young) to proceed efficiently to this potentially curative option. In a nonmalignant disease, such as AA, it is advantageous to use strategies to minimize GVHD.[21] Multiple approaches are used toward this goal. **Table 1** reviews results of these studies. As in all of BMT, multiple factors require evaluation before alternative donor BMT in AA.

THE ROLE OF HIGH-DOSE CYCLOPHOSPHAMIDE IN THERAPY FOR APLASTIC ANEMIA

High-dose cyclophosphamide (HiCY) (50 mg/kg/d $\times$ 4 days) has as unique history in the context of AA for transplant and nontransplant therapies. **Fig. 1** shows the role of cyclophosphamide over the past six decades for AA. The first successful allogeneic BMT in a human was performed for SAA following conditioning with HiCY.[22] Shortly afterward, reports of complete hematopoietic recovery with host hematopoiesis following allogeneic BMT for SAA began to trickle into the literature.[23,24] This suggested that HiCY, with its stem cell–sparing yet highly lymphocytotoxic properties, could achieve durable complete responses in SAA. This hypothesis was confirmed