Upfront Matched Unrelated Donor Transplantation in Aplastic Anemia

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KEYWORDS

- Aplastic anemia • Hemopoietic stem cell transplantation (HSCT)
- Matched sibling donor • Matched unrelated donor

KEY POINTS

- Idiopathic severe aplastic anemia (SAA) is a rare condition, and hemopoietic stem cell transplantation (HSCT) remains the only curative therapy.
- HSCT is considered first-line treatment in patients less than 35 years old with SAA with a matched sibling donor (MSD).
- Current best practice is less clear in those without an MSD. Immunosuppressive therapy (IST) has traditionally been thought of as first-line treatment in those without an MSD; however, there remains a significant risk of relapse and clonal evolution.
- Outcomes following matched unrelated donor (MUD) HSCT in SAA have improved because of advances in the development of high-resolution HLA typing, developments in supportive care, and implementation of novel conditioning regimens.
- After careful discussion with the patient and parents, MUD HSCT could be considered first-line treatment in selected patients.

INTRODUCTION

Aplastic anemia (AA), defined by pancytopenia and a hypocellular marrow in the absence of reticulin fibrosis or abnormal infiltration, is a rare disorder with an incidence of approximately 2 per million in Europe.[1] Most cases are idiopathic, with T-cell–mediated destruction of hematopoietic stem cells thought to be the underlying pathophysiology. Without treatment, patients are likely to succumb to infection or hemorrhage. In this review, the authors discuss how to approach one of the outstanding questions in the management of patients with severe aplastic anemia (SAA): "What is the role of

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TREATMENT OF APLASTIC ANEMIA

Allogeneic hematopoietic stem cell transplant (HSCT) from an HLA matched sibling donor (MSD) is the preferred frontline treatment of pediatric and young adult patients with AA.[1,2] In those lacking such a donor, immunosuppressive therapy (IST) has historically been primary treatment, but with improved outcomes after transplants from matched unrelated donors (MUD), many centers now consider upfront MUD HSCT. Although historically MSD HSCT was associated with a higher overall survival (OS) than IST, this is no longer the case in children because of better salvage of IST failures. Recent studies from Japan and the European Blood and Marrow Transplantation (EBMT) indicate that frontline MSD HSCT leads to a better failure-free survival (FFS) than IST but not OS.[2–4] Therefore, because of the excellent OS seen in pediatric SAA, comparisons between IST and HSCT should focus on event-free survival (EFS) rather than OS.

The use of IST as treatment of AA originates from the observation of autologous marrow reconstitution in patients with graft failure who had undergone HCST with antithymocyte globulin (ATG) conditioning.[5] Current guidelines recommend horse antithymocyte globulin (h-ATG) with cyclosporine (CSA), because combination therapy is superior to ATG alone.[6] Pediatric studies using this combination have reported overall response rates of between 59.9% and 77%.[7–10] Factors influencing response rates are shown in **Box 1**.

The use of the more immunosuppressive rabbit ATG is not recommended outside of relapse/refractory cases because it has been associated with inferior outcomes compared with h-ATG.[8,11–13] Response to IST is evaluated between 3 and 4 months after treatment. If there has been a response, CSA can be weaned slowly from 6 months with frequent monitoring of blood for signs of relapse. Between 15% and 25% of children remain CSA dependent.[9] The monitoring required and ensuing subnormal blood counts may have a detrimental effect on children and their families' quality of life. Relapse rates have been reported in 11.9% to 33% of patients undergoing IST. Current practice is to use MUD HSCT for those failing one course of IST, due to superior EFS compared with a second course of IST.[14] In patients who have had a prior response to IST, in those without a suitable donor, a repeat IST has a response rate of 60% to 70%.[13,15] Between 10% and 15% of patients who have undergone IST

Box 1
Good prognostic factors for response to immunosuppressive therapy

- Severity (very severe aplastic anemia better than severe aplastic anemia)
- Younger age
- Higher reticulocyte and lymphocyte count at diagnosis
- Male gender
- Leukocyte count $<2 \times 10^9$/L
- Early treatment
- Minor paroxysmal nocturnal hemoglobinuria clone
- Longer telomere length