

Aplastic Anemia in the Orient

Seiji Kojima

*Department of Developmental Pediatrics, Nagoya University Graduate School of Medicine,
Nagoya, Japan*

Abstract

Aplastic anemia (AA) is more common in Asia than in Europe or the United States. This may be due in part to the high incidence of hepatitis-associated AA in Asia. The management of AA has evolved rapidly in Japan during the last decade. Advances in the treatment of AA have largely been the result of prospective collaborative studies of immunosuppressive therapy and the large registry of bone marrow transplantation data. These studies have revealed several differences in clinical outcome between Western and Eastern patients, differences that may reflect the effects of genetic background on response to treatment or development of adverse effects.

In Europe and the United States, aplastic anemia (AA) is a rare disease, with annual incidence ranging from 1.0 to 2.0 per million per year. However, in Asia, AA appears to be more common. In a population-based study, the incidence of AA in Thailand was found to be 3.7 per million. According to registration data from Taiwan and Japan, the incidence of childhood AA in those countries is 10.0 and 3.2 per million, respectively, and about 25% of children with AA in Taiwan and 10% of those in Japan have a history of recent acute hepatitis. Such a high incidence of hepatitis-associated AA may be a contributing factor in the higher incidence of AA in Asia.

The management of severe AA (SAA) evolved rapidly during the 1990s. These advances in the treatment of AA have largely been the result of prospective collaborative studies. The Japan Childhood Aplastic Anemia Study Group was founded in 1992 to conduct prospective multicenter trials for childhood AA. As of April 2002, more than 400 children with acquired AA had been enrolled into 2 consecutive protocol studies: childhood AA-92 and AA-97. In the childhood AA-92 study, a prospective multicenter trial was conducted, comparing treatments using antithymocyte globulin (ATG), cyclosporine (CyA) and danazol, with or without globulin colony-stimulating factor (G-CSF). The addition of G-CSF to immunosuppressive therapy (IST) produced no benefits in terms of hematologic response, incidence of febrile episodes, documented infections, or actual survival rates.

Recently, several studies have suggested that long-term survivors of AA treated with IST are prone to developing myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). We prospectively assessed risk factors for developing MDS/AML in 113 patients enrolled in the childhood AA 92 study. Twelve patients developed MDS between 9 and 81 months after diagnosis of AA. The incidence of MDS at 8 years after diagnosis was $14\pm 7\%$. In the multivariate analysis of risk factors, the number of days of G-CSF therapy and non-response to IST were statistically significant risk factors. Our results suggest a close correlation between long-term use of G-CSF and secondary MDS/AML in non-responders to IST.

Based on the results of the childhood AA-92 study, we started the next multicenter trial, childhood AA-97. In that prospective study, we compared the efficiency of repeated IST and stem cell transplantation from an alternative donor in non-responders to first-line therapy. Thirty-seven patients were evaluated for response to second-line therapies. Only 3 out of 24 patients showed trilineage response to second IST. Thirteen patients received SCT from alternative donors, as follows: 10 from unrelated bone marrow donors, 2 from unrelated cord blood donors, and 1 from an HLA-mismatched sibling. Failure-free survival (FFS) was defined as survival with response. The following outcomes were considered treatment failure: death, no response within 6 months, disease progression, and relapse. The estimated FFS at 2 years after the start of second-line therapies was $69\pm$

13% for the SCT group and 9±6% for the IST group. The results of the AA-97 study suggest that alternative-donor SCT offers a better chance of FFS than repeated IST in non-responders to first IST.

Bone marrow transplantation (BMT) is generally considered the treatment of choice for AA patients with a suitable donor in their family. Due to early encouraging results, cyclophosphamide (CY) and ATG have been widely used to precondition patients with severe AA who receive transplants from HLA-matched siblings. Recently, we analyzed results for 40 children with acquired AA who underwent transplantation preceded by preconditioning with a CY/ATG regimen. Unexpectedly, we found a high incidence of graft rejection and mixed chimerism. Eight (20%) of the 40 patients experienced either early (n=1) or late (n=7) graft rejection. We concluded that the CY/ATG regimen is not sufficient to achieve durable engraftment in Japanese patients with AA who receive transplants from HLA-matched siblings.

The optimum conditioning therapy and graft-versus-host disease (GVHD) prophylaxis for unrelated-donor

BMT to treat SAA has yet to be established. We analyzed the outcomes of 154 patients with SAA who received transplants from unrelated donors identified through the Japan Marrow Donor Program. The probability of 5-year survival was 56±11%, with a median follow up of 29 months. The incidence of grade III/IV acute GVHD and chronic GVHD was 18% and 30%, respectively, rates that are much lower than those reported in Western countries. Multivariate analysis revealed the following unfavorable factors: transplantation more than 3 years after diagnosis, patients older than 20 years, preconditioning regimen without ATG, and HLA-A or -B locus mismatching. Unlike the report from the National Marrow Donor Program in the United States, our results did not show HLA-DRB1 mismatching to be a significant risk factor for acute GVHD or overall survival. These differences in clinical outcome between Eastern and the Western patients may reflect the effects of genetic background on response to treatment or development of adverse effects.