

Aplastic Anemia in Children

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Acquired aplastic anemia (AA) is an uncommon, but serious disease characterized by pancytopenia and decreased bone marrow cellularity. Bone marrow transplantation (BMT) and intensive immunosuppressive therapy (IST) have improved outcome of AA in children, with long-term survival rates of 70 to 90%. Although BMT from an HLA-identical sibling donor is the treatment of choice for children with severe AA, this approach is limited by the availability of such donors. For patients who do not have a suitable donor, IST is used.

Advances in 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 2004, more than 400 children with acquired AA had been enrolled into 2 consecutive protocol studies. 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 granulocyte colony-stimulating factor (G-CSF). Although G-CSF accelerated neutrophil recovery, there was no difference in trilineage response or overall survival between the G-CSF group and the non G-CSF group.

Despite evident short-term efficacy, questions remain about long-term outcome of patients treated with IST. Concerns have focused on the high incidence of relapse and increased risk of clonal hematological complications such as paroxysmal nocturnal hemoglobinuria (PNH), myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Recent several studies have addressed these questions. Relapse was common in all these studies, but it did not influence survival. In 10 to 15%

of patients, evolution to MDS/AML was observed.

We analyzed long-term outcome of AA children registered into the childhood AA-92 study. The median observation time of surviving patients was 85 months, ranging from 69 to 121 months. Of the 77 patients with response, 27 had relapse 8 to 72 months after treatment. Among these 27 patients, 17 received a second course of IST with ATG and CyA. Half of the patients responded to the second therapy. Among the 9 non-responders, 5 received BMT from an alternative donor and 1 died. BMT was attempted as second-line therapy in 7 patients. Two of whom died of BMT-related toxicities. Thus, 24 patients survived after relapse.

New cytogenetic abnormalities appeared in a patients after IST, including monosomy 7 (3 patients), and trisomy 8 (3 patients). Five of these 9 patients had a dysplastic morphology. Because distinctive morphologic features of MDS were not found in 13 patients with trisomy 8 and 1 patient with del (13), MDS was not diagnosed for them. Malignant disease did not develop in any of these 4 patients during the follow-up period.

A total of 17 patients died between 1 and 107 months after diagnosis. Causes of death were BMT-related toxicities (7 patients), bacteremia/pneumonia (3), interstitial pneumonitis (2), MDS (2), intracranial bleeding (1) and other causes (2). We evaluated hematological values at the time of last follow-up. Among the 64 surviving patients who were treated with only IST, 47 (73%) showed complete response and 12 (19%) showed partial response. These results suggests that a significant proportion of patients are likely to be cured after IST. Alternative donor BMT offers a good chance of survival

for those who do not respond to a combined therapy with ATG and CyA.

Introduction of intensive IST combined with ATG and CyA has improved the outcome of patients with SAA. However, 30 to 40 % of patients fail to respond to IST, requiring second-line therapy. Treatment options for non-responders include re-treatment with immunosuppressive agents or stem cell transplantation from an alternative donor. There is no consensus on treatment for patients not responding to intensive IST. The Childhood AA-97 study was a prospective multicenter study comparing the efficacy of repeated IST and stem cell transplantation from an alternative donor in patients who failed to respond to the first IST. In Europe, it is popular to give a second course of ATG in patients who show no response. In a large retrospective study by the European Blood and Marrow Transplant (EBMT) Group, 90 of 213 patients (42%) responded to second course of IST with long-term survival rate of 69%. On the other hand, long-term survival rate was only 13% in 494 patients who did not respond to the first course of IST and did not receive further therapy.

Preliminary data disclose that the response rate to second IST was much lower in our study than that of European study. The reason for the discrepancy in response rate between the Japanese and European study is unknown. The timing of the evaluation of first IST is an important factor for analysis of the effectiveness of second IST. Because the European study is retrospective, difference in starting time makes it difficult to compare the response rate between the Japanese and European studies. Compared to the remarkable improvement in the outcome of patients with SAA, outcome of patients with non-severe AA has not improved over the last 10 years. The European Prospective study showed that the combination of ATG and CyA is superior to CSA alone in terms of the hematologic response for patients with non-severe AA. The AA-97 study will reveal whether addition of CyA to ATG treatment improves the response rate in patients with non-severe AA.

Hepatitis-associated AA (HAA) is a variant of acquired AA in which an episode of hepatitis precedes AA by a period of weeks to months.

Without suitable treatment, the prognosis of HAA is very poor. It has been suggested that immunological mechanisms are involved in the pathogenesis of HAA and immunosuppressive agents have been used effectively to treat HAA in a small study. We prospectively investigated 44 patients with HAA who were registered into AA-92 and AA-97 studies. Severity of disease was classified as very severe (n=25), severe (n=15) and moderate (n=4). Two patients died of cytomegalovirus (CMV) pneumonitis and one of fungal pneumonia within 3 months from initiation of treatment. Of 41 evaluable patients, 14 (34%) achieved complete response (CR) and 17 (41%) achieved partial response (PR), for an overall response rate of 75% after 6 months from initiation of treatment. A further 2 patients exhibited hematological response between 6 and 12 months. Seven non-responders to IST received bone marrow transplantation from unrelated HLA-matched donors and one patient underwent a second cycle of IST. Clonal cytogenetic abnormalities were detected in two patients; trisomy 8 and del (13), respectively. Distinct morphologic findings of MDS were not found in either of patients. The probability of overall survival at 8 years was $90.9 \pm 8.4\%$. Given the present results, we recommend IST with ATG and CyA as the treatment of choice for patients with HAA who lack an HLA-identical sibling.

It is difficult to increase response rate of IST to more than 70% even using an intensified regimen. Another approach may be necessary to break through this figure. Because the most frequent cause of death is transplant-related toxicity in patients who enrolled in our studies, it is particularly important to determine the optimal conditioning regimen for alternative donor transplant.