

First-line treatment for severe aplastic anemia in children: bone marrow transplantation from a matched family donor versus immunosuppressive therapy

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Supplementary methods

Between 1992 and 2009, a total of 599 consecutive children (younger than 17 years) with acquired SAA received BMT from an MFD or IST as first-line treatment in Japan; 213 patients with an MFD received BMT and were registered in the Transplant Registry Unified Management Program (TRUMP) conducted by the Japan Society for Hematopoietic Cell Transplantation, and 386 patients without an MFD were enrolled in the two consecutive prospective multicenter trials (AA-92/97) conducted by the Japan Childhood AA Study Group and were initially treated with IST. The disease was considered severe if at least two of the following were noted: neutrophil count $<0.5 \times 10^9/L$; platelet count $<20 \times 10^9/L$; or reticulocyte count $<20 \times 10^9/L$ with hypocellular bone marrow. AA was considered very severe if the criteria for severe disease were fulfilled and if neutrophil count was $<0.2 \times 10^9/L$.

IST

Three hundred and eighty-six patients were enrolled in the AA-92 (n=84) and AA-97 (n=302) trials, and all patients were initially treated with a combination of intravenous horse ATG (Lymphoglobulin; Genzyme, Cambridge, USA) at 15 mg/kg/day for 5 days and oral CyA at 6 mg/kg/day. The dose of CyA was adjusted to maintain trough levels between 100 and 200 ng/mL, and the appropriate dose was administered for at least 6 months. Granulocyte colony-stimulating factor (G-CSF) (filgrastim; Kirin, Tokyo, Japan) was administered intravenously or subcutaneously at $400 \mu\text{g}/\text{m}^2$ for 3 months to patients with very severe disease. Patients with severe disease were randomized to receive G-CSF in the AA-92 trial but were not given G-CSF in the AA-97 trial unless severe infection was documented. Response to IST was evaluated at 6 months after initiation of therapy. Complete response (CR) was defined as a neutrophil count $>1.5 \times 10^9/L$, a platelet count $>100 \times 10^9/L$, and a hemoglobin level $>11.0 \text{ g/dL}$. Partial response (PR) was defined as a neutrophil count $>0.5 \times 10^9/L$, a platelet count $>20 \times 10^9/L$, and a hemoglobin level $>8.0 \text{ g/dL}$ in patients with

severe or very severe AA. Overall response was defined as CR or PR at 6 months after IST. Relapse was indicated by the return of the peripheral blood cell counts to levels meeting the definition of severe AA and the requirement for blood transfusion.

BMT

A total of 213 children with SAA underwent BMT from an MFD as first-line treatment following the local protocols for conditioning regimens and GVHD prophylaxis (Table 2). The majority of patients (n=203) were transplanted with a graft from an HLA-identical sibling, while 10 patients received it from an HLA-matched parent (father or mother). The conditioning regimens were mainly based on high-dose (200 mg/kg) cyclophosphamide (CY) in combination with ATG and/or low-dose irradiation; 2-5 Gy of total body or thoraco-abdominal irradiation, or 3-7.5 Gy of total lymphoid irradiation (158 patients). Fludarabine and 100-120 mg/kg of CY-based regimens were used in 44 patients. For small proportion of patients, myeloablative regimens were used. In total, ATG was included in the conditioning regimen in 87 patients, while irradiation was included in 129 patients. GVHD prophylaxis consisted mainly of CyA alone (23 patients) or in combination with methotrexate (174 patients). Other drugs, including tacrolimus, were used in 16 patients. Ex vivo T-cell depletion was not used for any patient. Acute GVHD was evaluated according to standard criteria in patients who achieved engraftment, and chronic GVHD was evaluated according to standard criteria in patients who achieved engraftment and survived for 100 days after transplantation.