

Aplastic anemia; epidemiology and clinical trial in Japan

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Aplastic anemia (AA) is a bone marrow (BM) failure syndrome of heterogeneous causes. AA is an uncommon but serious disorder characterized by pancytopenia resulting from nonfunction of the bone marrow. Incidence of this disorder in Asian countries is thought to be higher than in western countries. 70-80 children are diagnosed of AA every year in Japan. It accounts for 13-16% of acute leukemia children. AA committee of the Japanese Society of Pediatric Hematology (Prof. Tsukimoto) conducted annual nationwide survey of children with bone marrow failure syndrome, such as AA (epidemiology, retrospective study). And also, the Japan Childhood Aplastic Anemia Study Group (Prof. Kojima) developed prospective clinical trials for an acquired AA with immunosuppressive therapy (IST). Results from these two studies will be discussed in this session.

< Epidemiology >

As of 2002, 760 idiopathic AA children (diagnosis year 1988-2000) have been registered and followed up. Numbers of newly diagnosed patients in each year ranged from 45-82. Severe AA patients accounted for 53% of these patients. Over 80% of patients who were diagnosed after 1994 underwent BM cell chromosomes analysis, and 9 of 336 patients showed abnormalities at their presentation. The survival rate of very severe (neutrophil count $<0.2 \times 10^9/L$) and severe AA patients who were diagnosed after 1994 improved (KM survival rate $86.7 \pm 5.3\%$, $87.5 \pm 3.8\%$, respectively); however that of moderate and mild patients did not. It should be of concern that some of the mild patients died over 5 years later. Prognosis of allogeneic BM transplantation from HLA matched siblings was good. If patients received HLA matched

unrelated donor (MUD) BM transplantation (JMDP provided) within 2 years, the prognosis was fair (KM survival 86.4% after the transplant).

Hepatitis associated AA (HAA) is one of acquired AA. Immune-mediated mechanism is thought to play an important role in BM aplasia. Pathogenic virus for hepatitis and BM aplasia has not been discovered yet. The incidence is 10-12% of idiopathic AA in Japan. Even if it is very severe type, HAA patient generally responds for IST well and recovers. However, a life threatening CMV interstitial pneumonia was reported in 2 patients who received IST should be remembered.

Diamond-Blackfan anemia (DBA) is a congenital pure red cell aplasia of unknown etiology that most commonly manifests in the neonatal period. This rare disease usually demonstrates a more favorable life expectancy than AA. 54 patients were diagnosed between 1988-1998, accounting for 8% of idiopathic AA, and only 3 patients had a familial occurrence in Japan. All patients received prednisolone and 47 patients received red cell transfusion, and 13 patients underwent hematopoietic stem cell transplantation (HSCT) (MFD BM 4, MUD BM 3, miss-MUD BM 2, MFD CB 2, miss-MUD CB 2)(disease free 11, rejection 1, death 1). The cumulative probability of a transfusion-free state was 69% at 5 years. (Int. J. Hematol 79,2004)

Fanconi anemia (FA) is a typical congenital BM failure syndrome and characterized by frequent AML or solid tumor development. 55 patients were diagnosed between 1990-1999. 36 of 55 patients were made an analysis of clinical characteristics. 13 of the 36 patients had a family history of FA. 2 developed into solid tumors and 7 patients had features of myelodysplastic syndrome

(MDS). 12 patients underwent HSCT, and 16 patients died within 8 years after diagnosis. Chromosomal fragility test was performed in 23 patients and genetic analysis was examined only in 7 patients, at that moment.

Secondary MDS/AML in typical acquired AA patients is one of big clinical issues. We observed 11 patients who received IST and high dose rhG-CSF developed MDS/AML (Blood 90,1997). Monosomy 7 is the most frequent and has the worst-prognosis chromosome abnormality. In the cases of MDS/AML following IST, the primary issue seems to be whether the patients already had an MDS clone at the time of diagnosis or whether secondary MDS was related to the therapy itself. Further studies are required to clarify the pathogenesis of the clonal disorder in patients with acquired AA.

< Clinical trial: Childhood AA-92 study >

A prospective multicenter trial of 119 children with newly diagnosed AA was conducted in 1992 (Childhood AA-92), comparing treatment using antithymocyte globulin (ATG), cyclosporine (CyA), and danazol (DAN) with or without rhG-CSF. All children with very severe AA received rhG-CSF (VSAA group, n=50). The other 64 children (non-very severe AA)(severe AA 36, non-severe AA 28) were randomized to receive ATG, CyA, DAN, and rhG-CSF (G-CSF + group, n=33) or ATG, CyA, and DAN without rhG-CSF (G-CSF – group, n=31). After 6 months, hematologic response rate was 71%, 55%, 77% in the VSAA, G-CSF +, and G-CSF – group, respectively. Response rate was 65% in non-very severe AA patients. The probability of survival at 4 years was 83 ±7% in VSAA group, 91±5% in the G-CSF + group, and 93±6% in the G-CSF – group. We concluded that IST is effective for AA, and non-very severe AA patients do not need rhG-CSF combined with IST, because no difference was observed in survival rate and an incidence of infection between G-CSF + and G-CSF – group. (Blood96,2000)

Long-term outcome of acquired AA children treated with Childhood AA-92 study was observed in 2003. 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 of >11 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 of >8.0 g/dl. Relapse was indicated by the return of the PB counts to levels meeting the definition of SAA and/or the requirement for blood transfusion. Response rate was 71% at 6 months in vSAA patients, 65% in SAA/nonSAA patients, respectively as mentioned above. No patient responded after 6 months. Therefore, 75 responders and 29 non-responders at 6 months were analyzed their OS, relapse rate (RR), and treatment-failure-free survival (TFFS). The median observation time of surviving patients is 80 months, ranging from 44 to 130 months.

Among 119 patients, 37 patients received BMT and 17 patients died during an observation period. The OS was $79.2 \pm 6.7\%$ at 9 years, but has not reached plateau. The RR was $27.7 \pm 4.9\%$. There is no statistically significant difference in OS between the responders and non-responders ($90.7 \pm 3.4\%$ vs. $55.1 \pm 23\%$, $p=0.09$). Of the 75 responders, 22 patients relapsed and the RR was $30.5 \pm 5.5\%$ at 9 years. 14 patients received 2nd ATG therapy and 5 of them responded. 10 of the 22 patients with relapse received MUD BMT and 7 are alive. TFFS of the 75 was $67.3 \pm 5.3\%$. OS after relapse was $75.9 \pm 9.5\%$. New clonal abnormalities appeared in 9 of 119 patients ($10.0 \pm 3.2\%$ KM probability): monosomy 7(3 patients), trisomy 8(3 patients), trisomy 9, trisomy 11, del (13)(1 patient each). We did not observe any patients with clinical PNH. Among 65 surviving responders, 33(51%) have CR and 26(40%) PR at last follow-up time.

Our data demonstrate that IST is effective for children with acquired AA, but relapse and secondary clonal disease are common. Effective 2nd line treatment should be developed.