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Stem cell transplantation for aplastic anemia and myelodysplastic syndrome

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Summary:

Stem cell transplantation (SCT) from a histocompatible sibling is treatment of choice for severe aplastic anemia. Survival rates have been reported to be as high as 90% for children. Immunosuppressive therapy (IST) is employed in patients who are not candidates for SCT due to donor unavailability. The addition of cyclosporin A to antilymphocyte globulin has improved the response rate to 70–80%, and survival at 5 years among responders is about 90%. In all, 30% of patients treated by IST suffer from relapse, but long-term prognosis does not appear to be affected by this complication. Juvenile myelomonocytic leukemia (JMML) shares both myelodysplastic and myeloproliferative features. Survival (10-year) of patients with JMML without SCT is only 6%. Children with JMML should be transplanted early in the course of their disease. Conditioning regimen composed of three alkylating agents, busulfan, cyclophosphamide and melphalan has been favored by the EWOG-MDS and EBMT-Pediatric WP in the second half of the 1990s. SCT using this conditioning regimen is capable of curing approximately 50% of patients with JMML. More than 70% of patients with refractory cytopenia and more than 50% of children with advanced MDS are cured of by the early performed allogeneic SCT.

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Acquired aplastic anemia

Acquired aplastic anemia is a rare disease with an annual incidence of two new cases per million inhabitants in Europe. In most patients with acquired aplastic anemia, the lymphocytes are responsible for the destruction of hematopoiesis. The result of this immune process is destructive with Fas-mediated CD34+ cell death.[1] Stromal function and growth factor production are normal in almost all patients with aplastic anemia. A significant history of radiation, benzene, or chloramphenicol use is very unusual among patients with acquired bone marrow failure. Hepatitis-associated aplastic anemia constitutes 2–5% of all cases of aplastic anemia in the West. Aplastic anemia follows an acute attack of hepatitis non-A, -B, -C, and is often fatal if untreated. Adolescent boys and young men are most often affected. Response to immunosuppressive therapy (IST) strongly suggests that immunologic mechanisms mediate the marrow aplasia.[2] Fanconi anemia has to be excluded by chromosomal breakage or cell cycle analysis in all children and young adults with bone marrow failure.

Stem cell transplantation (SCT) from an HLA-identical sibling donor for aplastic anemia

SCT from a histocompatible sibling usually cures the underlying bone marrow failure. Survival rates have been reported as high as 90% for children. The current standard conditioning regimen is high-dose cyclophosphamide $50\,mg/kg \times 4$ and antithymocyte globulin (ATG) with methylprednisolone. This preparative regimen is nonmyeloablative and highly immunosuppressive to prevent graft rejection and graft-versus-host disease (GVHD). The recommended post-transplant immunosuppression is cyclosporine A 5 mg/kg/day, starting on day –1 and continued for 12 months with tapering beginning at 9 months to prevent late graft failure, and a short course of methotrexate $15\,mg/m^2$ on day +1, then q $10\,mg/m^2$ on days +3, +6, and +11.[3] The outcome of SCT in aplastic anemia is worse with peripheral blood rather than bone marrow for source of stem cells. Fertility is preserved and the risk of solid tumors is not significantly increased after SCT for aplastic anemia.

Immunosuppressive therapy

IST is employed in patients who are not candidates for SCT due to lack of a sibling donor. The addition of cyclosporine

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A to antilymphocyte (ALG) or antithymocyte (ATG) globulin has improved the response rate to 70–80%, with survival at 5 years among the responders being about 90%.[4,5] Horse ATG is given for 5 days. The rabbit preparation is usually reserved for second or subsequent courses.[6] Response is rarely achieved before 3 months. Adding granulocyte-colony stimulating factor (G-CSF) to ATG and cyclosporine A will probably reduce the risk of infection during the 3 months preceding hematological recovery.[4] If there is no response to the first course of ATG, it is recommended to give another course, however not earlier than 3 months after the first course. There is a 60% chance of response to a second course of ATG.[7] When the patient has achieved a response and the blood count plateaued for at least 6 months, a slow tapering of cyclosporine can be considered.[6] In all, 30% of the patients treated by IST will relapse; however, the long-term prognosis does not appear to be affected by this complication.[8] Incomplete responses, frequent relapses, and cyclosporine dependence are probably evidence of a chronically disordered immune function. A further problem is the development of late clonal diseases. The risk of developing a clonal disorder (clinically overt paroxysmal nocturnal hemoglobinuria) or a malignant disease (myelodysplastic syndrome (MDS), acute myeloid leukemia (AML)) is 25% in adults and children followed long-term. Five-year survival after IST is excellent, but only a minority of the patients is cured. At 11 years, survival was between 50 and 60% in a group of 84 patients treated with ATG with or without cyclosporine A.[9] In the long run, SCT from an HLA-identical sibling donor is superior to IST in aplastic anemia. In this setting, durable cure can be expected from SCT, while IST usually does not lead to complete and stable recovery.[9,10]

SCT from unrelated donors

Survival of patients undergoing unrelated-donor SCT is lower due to higher risk of rejection, GVHD, and infection caused by delayed immune system reconstitution. In many cases, a myeloablative regimen incorporating irradiation has been employed. More recent data from a relatively small number of patients show reduced transplant-related mortality (TRM) when only fully matched donors or donors matched for HLA-DRB1 are used and more immunosuppressive regimens including fludarabine as a component are employed.[11] SCT from a matched unrelated donor (MUD) may be considered in children with severe aplastic anemia who have failed one to two courses of ATG and who have fully matched donor and no evidence of active infection.[6] High marrow cell dose is essential.

Myelodysplastic syndrome

MDS constitutes 5% of all malignant hematological disorders in children.[12] This rare disease constitutes a heterogeneous group of clonal stem cell disorders characterized by ineffective hematopoiesis with evident morphologic abnormalities. Blood cytopenia often involves all three lineages with morphologically and functionally abnormal cells. The bone marrow is usually hypercellular and displays characteristic dysplastic features and often an increased percentage of myeloblasts. Three major diagnostic groups are recognized:

(1) juvenile myelomonocytic leukemia (JMML), previously named chronic myelomonocytic leukemia or juvenile chronic myeloid leukemia;
(2) myeloid leukemia of Down's syndrome – a disease with distinct clinical and biological features encompassing both MDS and AML and occurring in Down's syndrome;
(3) MDS occurring either *de novo* or as a complication of previous therapy or a pre-existing bone marrow disorder (secondary MDS).

The main subtypes of MDS are: refractory cytopenia (RC), previously known as refractory anemia (RA); RA with excess of blasts (RAEB); and RAEB in transformation (RAEBt). Cytogenetics and serial assessments of the patients are essential adjuncts to morphology both for diagnosis and classification.[13] Owing to the rarity of childhood MDS, an international collaborative effort is necessary to facilitate sufficient clinical information, collect adequate material for research studies, and enroll enough patients on clinical trials. An example of a successful international collaboration is the history of the European Working Group on Myelodysplastic Syndromes in Childhood (EWOG-MDS).[14]

Except for children with Down's syndrome and myeloid leukemia, there is only anecdotal evidence for the cure of MDS by intensive chemotherapy alone, that is, without subsequent SCT. Conventional therapy is apparently unlikely to eradicate the primitive pluripotent cells involved in MDS. With a very few exceptions, SCT seems to be the only curative treatment. Patients should be grafted early in the course of their disease.

SCT for JMML

JMML, a disorder with myeloproliferative features, is primarily observed in infancy and early childhood. In a large series of JMML patients, the median survival without SCT was 1 year. At 10 years, the probability of survival for nontransplanted patients was 6%. Prognostic factors for the length of survival without SCT were the platelet count and age at the time of diagnosis, as well as the level of HbF. While all patients with a platelet count of $<33 \times 10^9$/l died within 1 year after diagnosis, 70% of those with a higher platelet count, age <2 years, and a HbF $<15\%$ were still alive 3 years after diagnosis. The karyotype did not influence survival significantly.[15] Children with JMML should be transplanted early in the course of their disease. High-risk patients according to the platelet count, age, and HbF level may be candidates for experimental SCT (haploidentical family donor), if an HLA-identical donor is not readily available. Recently, the outcome of 100 children with JMML given allogeneic SCT after a preparative regimen including busulfan, cyclophosphamide, and melphalan has been published. In all, 48 and

52 children were transplanted from an HLA-identical relative or an unrelated donor, respectively. The 5-year cumulative incidence of TRM and leukemia recurrence was 13 and 35%, respectively. The 5-year probability of event-free survival (EFS) for children given SCT from either a relative or an unrelated donor was 55% for the former and 49% for the latter group. In multivariate analysis, age greater than 4 years and female sex predicted poorer outcome.[16] If relapse occurs, a second SCT may be curative. Some patients who relapsed early following SCT were able to achieve remission following withdrawal of IST with the subsequent development of GVHD, providing the evidence of a graft-versus-leukemia (GVL) effect for JMML.[17]

SCT for primary and secondary MDS

A retrospective study of 67 children with RA showed that, in contrast to the hematological picture of RA in adults, 44% of the children had a hemoglobin level at diagnosis of more than 10 g/dl. The median white blood cell count and absolute neutrophil count were 3.6 and 0.9×10^9/l, respectively. In all, 75% of the patients were thrombocytopenic. The bone marrow was hypocellular in 39% of the cases. These findings suggest that RC is a more suitable name than RA. The results of cytogenetic analyses indicated that monosomy 7 is the most frequent chromosomal aberration in RC observed in 50% of the patients in this retrospective study. Patients with monosomy 7 had a significantly higher estimated probability of progression to advanced MDS compared to patients with other chromosomal abnormalities or a normal karyotype. The probability of survival at 15 years was 48%.[18] SCT is the treatment of choice. This should be performed before the blast count has increased to more than 10%, as chemotherapy prior to SCT should be avoided. Dependence on blood product transfusions can hasten the decision on timing of SCT.

Most cases of RAEB and RAEBt eventually progress to myelodysplasia-related AML. While some patients with RAEB have stable disease for several months, others progress to RAEBt and AML early. British investigators reported that the outcome of children with RAEBt enrolled in AML studies is comparable to that of primary AML, while the outcome of those with RAEB is significantly worse. However, we believe that this observation at least in part depends on the inclusion of typical *de novo* AML patients in the MDS group because of low blast count. Chemotherapy fails in patients with monosomy 7.[19]

In all, 28 patients with RC, 22 RAEB, and 39 RAEBt/AML have been enrolled onto the prospective EWOG-MDS/EBMT study, using busulfan, cyclophosphamide, and melphalan as the preparative regimen to allogeneic SCT. A matched family donor was used in 35 cases, and matched unrelated volunteer in 54. The median observation time for the surviving patients was 12 months. TRM was 14% for the family-donor transplants and 36% for the MUD transplants ($P = 0.01$), whereas no significant difference was observed for relapse rate between both groups (13% *vs* 17%, respectively). The EFS was 75% for children with RC, 49% for RAEB patients, and 60% for those with RAEBt/AML.[20] Patients with RAEB, RAEBt, and AML, who had received prior AML-type induction therapy, had a similar outcome compared to those who had not, with EFS at 4 years of 47 and 61%, respectively, ($P = 0.08$). There was no difference in EFS in patient groups with blasts <5, 5–19, or >20%. Indeed, AML-type induction therapy before SCT may not be warranted for children with advanced-stage primary MDS.[21] In view of the fact that TRM is the major cause of treatment failure in patients with RC, preparative regimens with reduced intensity are attractive.[22]

AML preceded by MDS can be expected to develop in 3–10 percent of the patients who receive alkylating agents as part of the therapy for their primary cancer. It is often associated with deletions of chromosomes 5 and 7. The prognosis of these patients is considerably worse than that of the patients with a primary MDS/AML. SCT performed as soon as possible, once the diagnosis of secondary MDS has been established, might improve the prognosis. The outcome of 23 patients with secondary MDS treated on the ongoing SCT trial of the EWOG-MDS has been reported. At 3 years, the probabilities for EFS, relapse, and TRM were 57, 14, and 33%, respectively. There were no significant differences in EFS according to the type of primary disease, karyotype, highest FAB subtype, or percentage of blasts at SCT.[23]

Conclusions

Allogeneic SCT appears to be the single curative strategy for childhood MDS. Previous reports on the efficacy of SCT refer to only small numbers of patients treated with a variety of myeloablative regimens and GVHD prophylaxis schemes. A busulfan-based intensive conditioning regimen seems to offer a better chance for cure in comparison with TBI-based therapy. GVL effect has an active role in the control of MDS. This may prove important in the design of GVHD prophylaxis regimens, and suggests that aggressive treatment of GVHD may increase the likelihood of relapse. In addition, immunotherapy including infusions of donor-derived lymphocytes may also prove useful in patients who relapse after SCT.

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