# STEM CELL TRANSPLANTATION FOR A MYELODYSPLASTIC SYNDROME IN CHILDREN

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## ABSTRACT

The myelodysplastic syndrome (MDS) is a rare, clonal disorder of pluripotent stem cells in children and is characterized by ineffective haematopoiesis, morphologic abnormalities in one or more cell lines in a usually cellular bone marrow, and by predilection for the acute leukaemia. A large proportion of children with MDS present associated clinical abnormalities. Allogeneic stem cell transplantation (SCT) is the only definitive cure for this heterogeneous group of lethal disorders. Results with SCT have been difficult to interpret due to the variability of conditioning regimens, types of donors, and pretransplant therapy. In many series, the outcome with donors other than matched siblings has been extremely poor. The optimal pre-transplant therapy and conditioning regimen for SCT in MDS have not yet been defined. The establishment of several international working groups will eventually help to elucidate the pathogenesis of childhood MDS and will evaluate new treatment strategies to improve their clinical outcome.

## CLASSIFICATION, ETIOPATHOGENESIS

The myelodysplastic syndrome (MDS) accounts 5-10% of all malignant haematological disorders in children [1]. This rare disease is composed of a heterogeneous group of clonal stem cell disorders, characterized by ineffective haematopoiesis with evident morphological abnormalities. Blood cytopaenia often involves all three lineages with morphologically and funcionally abnormal cells. The bone marrow is usually hypercellular, and displays characteristic dysplastic features, often with an increased percentage of myeloblasts. The French-American-British group (FAB) proposed a classification of MDS comprising five subgroups: refractory anaemia (RA), RA with ringed sideroblasts (RARS), RA with excess of blasts (RAEB), RAEB in transformation (RAEBt), and chronic myelomonocytic leukaemia (CMML) [2]. In children, the term CMML was replaced by the term 'juvenile myelomonocytic leukaemia (JMML)'. The distinction between the subgroups is based upon the number of blasts and monocytes in the blood, the number of ringed sideroblasts and blasts in the bone marrow, and the presence of Auer rods. With a few exceptions, the FAB classification can be successfully applied to childhood cases.

Today evidence has accumulated to support the concept that MDS is not only, preleukaemic phase of acute myelogenous leukaemia (AML), but it also represents a distinct haematological disorder, as reflected in different responss to therapy in MDS and AML. MDS involves pluripotent stem cells, whereas AML often involves more mature progenitor cells. Differences in cytogenetics and in the response to therapy between MDS and AML, reflecting fundamental biological differences, and thus justifies the morphologically based distinction between the two conditions proposed by the FAB group. Cases with blast counts close to 30%, whether classified as RAEBt or AML, may be quite similar from the biological point of view. Cases with a low blast cell count and AML-specific translocations may fit better a classification of AML, and should be treated as de novo AML [3].

There seem to exist major differences between childhood and adult MDS. RAEB/RAEBt and JMML dominate in childhood, whereas RARS, being common in older adults, is extremely rare in childhood. RA in children appears to have a higher rate of progression to leukaemia and a shorter time to progression. Monosomy 7 is the abnormality most frequently found in children. Predisposing conditions are more frequent in children than they are in adults. Most children transform to a more aggressive form of MDS or to AML within the first year following presentation. Children with RA may have a stable clinical condition lasting several years before progression.

## CYTOGENETICS

Cytogenetic abnormalities of the bone marrow cells are found in the majority of patients with MDS. Monosomy 7 is by far the most commonly encountered abnormality in children, whereas translocations, unlike in AML, are uncommon. Trisomy 8 is the second most common abnormality. Sequential cytogenetic examinations are recommended because clonal evolution is frequently encountered during the progression of the disease. Monosomy 7, as the sole abnormality in children, is apparently associated with a relatively long median survival. A stable disease lasting several years was documented in more than half of the patients with RA or RAEB and monosomy 7 [4]. Children with monosomy 7 alone had a superior survival rate than those with monosomy 7 and other cytogenetic abnormalities. The reverse was found in AML with monosomy 7 alone (3-y survival 13%) [4].

## PREDISPOSING CONDITIONS

At least one third of the children who develop any form of MDS suffer from genetically predisposing syndromes, whereas secondary and therapy-related forms of MDS are comparatively rare.

The risk of AML or MDS is approximately 10% in childen with *severe aplastic anaemia* not treated with stem cell transplantation (SCT) and approximately 7,5% in children with severe forms of *congenital neutropenia* at least 48 months from the diagnosis and G-CSF administered for a period of 24 months (5). It was especially MDS associated with monosomy 7 that has been fully documented.

*Familial bone marrow monosomy 7* has been observed in at least 10 kindreds. Clinicians should always be aware of the possibility that a child with MDS or AML and monosomy 7 may be the first one in an affected family. Therefore, potential sibling donors have to be carefully evaluated before they are eligible for SCT.

AML in children with the *Down syndrome* may be preceded by MDS in 30 to 60% of cases. MDS in children with the Down syndrome is, unlike MDS in other children, frequently associated with isolated thrombocytopenia as the presenting feature, and trisomy 8 as the most common acquired cytogenetic abnormality. MDS in the Down syndrome occurs virtually always during the first four years of life. AML that evolves from MDS in children with the Down syndrome responds very well to chemotherapy [6].

MDS was reported in 5-10% and AML in 10% of patients with *Fanconi anaemia.* RA and RAEB have been predominantly associated with this DNA repair deficiency syndrome. Fanconi anaemia should be excluded at the diagnosis of MDS. In the case of SCT a reduced-intensity conditioning regimen should be used due to a high risk of post-transplant toxicity in these patients.

Children with *neurofibromatosis type 1* account for approximately 15% of children with JMML.

## THERAPY

The treatment options of childhood MDS are at present very limited. Treatment with intensive chemotherapy (AML protocols) is associated with a high rate of cytopenia related deaths and a low remission rate. Those with remission often relapse within two years (7). With the exception of children with the Down syndrome there is only anecdotal evidence for the cure of MDS by intensive chemotherapy not followed by SCT. Conventional chemotherapy is apparently unlikely to eradicate primitive pluripotent cells involved in MDS, rendering the therapy non-curative. Consequently, myeloablative therapy supported by an allogeneic stem cell infusion may be necessary to cure childhood MDS. With very few exceptions SCT seems be the only curative treatment. More children than adults are likely to benefit from SCT. SCT is associated with a survival rate of 30 – 60%. The high rate of relapse in advanced FAB stages has led to graft patients earlier in the course of the disease. Patients with RA, RAEB or JMML and monosomy 7 treated with SCT without prior chemotherapy had a 3-year survival rate of 73% [4].

## STEM CELL TRANSPLANTATION FOR JMML

JMML – a disorder with myeloproliferative features primarily observed in infancy and early childhood – is characterized by prominent hepatosplenomegaly, frequent skin involvement, leukocytosis, monocytosis, and presence of immature precursors in peripheral blood. It is characterized by a reversion to a fetal type of erthropoiesis and the spontaneous exuberant proliferation of neoplastic macrophage/monocyte progenitor cells *in vitro.* The characteristic spontaneous formation of extremely high numbers of abnormal colony-forming unit cells (CFU-GM) colonies *in vitro* are probably generated through an autocrine or paracrine production of cytokines, such as interleukin 1 and GM-CSF. The most important

pathophysiological feature seems to be the neoplastic cells hypersensitivity to GM-CSF.

JMML alone accounted for 2-3% of all leukaemias, and has previously been referred to as chronic myelomonocytic leukaemia (CMML) or juvenile chronic myelogenous leukaemia (JCML). A disease with monosomy 7 has also been referred to as an infantile monosomy 7 syndrome.

In a large series of patients with JMML, the median survival rate without SCT was one year. At 10 years, the probability of survival for untransplanted patients is 6%. Prognostic factors for the length of survival without SCT were the platelet count at the time of diagnosis, age and HbF. While all patients with a platelet count $< 33 \times 10^9/l$ died within one year after diagnosis, 70% of the children with a higher platelet count, age $< 2$ years and an HbF $< 15\%$ were still alive 3 years after diagnosis. Karyotype did not influence survival significantly [8].

Most of the children classified as JMML treated with AML-like schedules did achieve a remission, but virtually all of them relapsed within two years. In a retrospective analysis of treatment modalities other than SCT, the survival of the intensively treated group was similar to that of children receiving less intensive treatment (6-mercaptopurin). Splenectomy in children without SCT can significantly prolong survival, while the role of splenectomy in SCT is less clear. It is current practice to remove large spleens prior to SCT.

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 an experimental SCT (haploidentical family donor), if HLA-identical donor is not readily available. Good risk patients have sufficient time to search for an optimal SCT donor. SCT is capable of curing approximately 30% of patients, with a significant advantage for those transplanted using an HLA–compatible family donor [9,10]. Busulfan-based myeloablative therapy should be preferred, since it seems to offer a better EFS due to a greater antileukaemic activity. Busulfan pharmaco-kinetics vary with patient's is age, careful monitoring of busulfan plasma levels should be carried out in all patients, and especially in those under 3 years of age. In children with JMML given allogeneic SCT from HLA-compatible family donor, a reduction in the intensity and/or duration of GVHD prophylaxis can significantly contribute, through an enhanced antitumour effect, to successful leukaemia control. Children less than 2 years of age at SCT had an improved EFS, which

reproduces the more favourable outcome in younger patients.

The risk of a relapse has been very high following SCT. If a relapse occurs, a second SCT may be curative. Some patients who relapsed early following matched unrelated donor (MUD) SCT for JMML, were able to achieve remission following withdrawal of immunosuppressive therapy and subsequent development of GVHD, providing evidence of a graft-versus-leukaemia (GVL) effect for JMML [11]. Immunotherapy including infusions of donor-derived lymphocytes may also prove useful in patients who relapse after SCT.

## STEM CELL TRANSPLANTATION FOR RA, RAEB, RAEBT

Most cases of RAEB and RAEBt eventually progress to AML. While some patients with RAEB haver stable disease for several months, others progress to RAEBt and AML early. The 3-year survival in children not treated with SCT is approximately 10% [12]. As most patients with RA will progress to leukaemia, SCT is the treatment of choice. SCT should be performed before the blast count has increased to more then 10%, as chemotherapy prior to SCT should be avoided. Dependency on blood product transfusions can fasten the decision about timing of SCT.

Allogeneic SCT is the treatment of choice for children if compatible sibling or matched unrelated donor is available. A greater than 50% event-free survival rate has been achieved in children with MDS, including RA, who were transplanted without the preceding induction therapy. Patients with RA and stable RAEB are unlikely to benefit from intensive chemotherapy before SCT, and it is still an open question whether pre-transplant chemotherapy would improve the outcome in patients who have RAEBt [13,14]. The risk of transplant-related mortality may be higher in patients who received intensive chemotherapy prior to SCT. Patients without excess of blasts have a superior survival following SCT, although a 50% survival has been reported following SCT in previously untreated RAEBt. There are no randomized studies, which would compare the results of induction chemotherapy versus SCT as the first line treatment in MDS.

If no HLA-identical donor is available, intensive AML-specific chemotherapy seems to be an option to improve survival without SCT.Younger age, normal karyotype, RAEBt morphology, and the presence of Auer rods are all associated with relatively favorable results of chemotherapy in adults.

There appears to be no significant difference in the outcome based on preparative regimen in this population of patients [15].

## THERAPY-RELATED MDS AND AML

AML preceded by the MDS can be expected to develop in 3 to 10 percent of patients who receive alkylating agents as part of their therapy for primary cancer. The risk of this type complication peaks 5 to 10 years after the start of chemotherapy, which is often associated with deletions of chromosomes 5 and 7. The prognosis in these patients is considerably worse than that in patients with primary AML. Therapy-related AML is biologically more aggressive and/or more resistant to treatment than spontaneous AML. Chemotherapy fails to achieve long-lasting remissions. SCT seems to offer a better chance for cure but at present the results are still disappointing [16]. Increased incidence of severe or moderately severe regimen-related toxicity is reported in patients transplanted for secondary AML and MDS. Patients with therapy-related AML conditioned with busulfan and cyclophosphamide have a higher risk of a relapse than do patients with *de novo* AML conditioned with the same agents [17]. Survivors of SCT for therapy-related leukaemia will be at a significant risk of developing third malignancies even in the absence of a familial cancer predisposition. Non myeloablative conditioning with donor lymphocyte infusion (DLI) post-transplant would be a reasonable option for further evaluation in this group of patients.

## CONCLUSIONS

Allogeneic SCT appears to be the only curative strategy for childhood MDS. Previous reports on the efficacy of SCT refer to only a 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. Graft-versus-leukaemia effect has an active role in 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 a relapse. In addition, immunotherapy, including infusions of donor-derived lymphocytes, may also prove useful in patients who relapse after SCT. Adoption of more effective methods of selecting unrelated donors can also improve treatment results. Further improvements in the ability to treat patients with this disorder will only be expected if patients are treated in a uniform manner in prospective clinical trials within the context of large cooperative groups in Europe (EWOG-MDS) and in North America (CCG/POG).

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