

## \* CHAPTER 37

# HSCT for myelodysplastic syndromes in children

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## 1. Introduction

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal disorders, accounting for less than 5% of all haematological malignancies of childhood (1). Childhood MDS include both variants shared with the adult population (i.e. RAEB, RAEB-t) and other disorders more typical of the paediatric age, such as juvenile myelomonocytic leukaemia (JMML) (1, 2). This latter disorder predominates in infants, the median age at diagnosis being 2 years (2). About 9% of patients with JMML are diagnosed before the age of 4 months, whereas less than 10% of patients are 6 years or older. In JMML, there is a male predominance with a male/female ratio of 2:1. Hypersensitivity to GM-CSF and pathological activation of the RAS-RAF-MAP (mitogen-activated protein) kinase signalling pathway play an important role in the pathophysiology of JMML. Allogeneic HSCT is the only curative approach for children with JMML, resulting in long-term survival in a significant proportion of patients receiving an allograft (2–5).

Childhood MDS other than JMML often occur in the context of congenital bone marrow failure syndromes, this fact representing a peculiarity of myelodysplasia occurring in the paediatric age group (1). HSCT is routinely offered also to all children with RAEB and RAEB-t, to paediatric patients with MDS secondary to chemo-radiotherapy, and to those with refractory cytopenia (RC) associated with cytogenetic anomalies or transfusion dependence (6).

## 2. Indications, results and risk factors

### 2.1. Juvenile myelomonocytic leukaemia

A number of different studies have reported that children with JMML can be definitively cured by an allograft (3–5). In the most recent study, which included the largest number of patients with JMML given allogeneic HSCT from either a histocompatible relative or from an HLA-matched/1-antigen mismatched donor, the probability of LFS was in the order of 50% (4). In multivariate analysis, age greater than 4 years and female sex predicted poorer outcome (4). Available data indicate that, in the more recent years, using an unrelated donor offers minimal or possibly no significant disadvantage as compared to employing an HLA-identical sibling (4). While one study reported a negative impact of monosomy 7 (7), the most frequent cytogenetic anomaly in JMML, on the probability of OS after HSCT, other larger analyses documented that neither monosomy 7 nor other cytogenetic abnormalities confer a poorer prognosis (3–5). Leukaemia recurrence represents the main cause of treatment failure in children with JMML treated by HSCT, relapse rate being as high as 50% (4).

Preparative regimens without TBI are particularly attractive for children with JMML since radiation-induced late effects, such as severe growth retardation, cataracts, hypothyroidism and neuropsychologic sequels may be especially deleterious for very young children. Moreover, in a retrospective analysis of the EWOG-MDS, busulfan-based myeloablative therapy offered a greater anti-leukaemic efficacy than TBI (3). The recommended preparative regimen of the EBMT/EWOG-MDS groups for children with JMML includes busulfan, cyclophosphamide and melphalan.

Splenectomy before HSCT, as well as spleen size at time of the allograft, did not appear to have an impact on post-transplantation outcome of children with JMML. Available data are not in favour of an indiscriminate use of splenectomy before transplantation, the potential advantages having to be weighed against the risks related to the procedure or to post-splenectomy infections (3, 5). The indication of performing splenectomy has to be carefully evaluated for each individual child, the presence of massive splenomegaly with evidence of hypersplenism and/or refractoriness to platelet transfusions being an argument for considering this procedure in order to promote engraftment, to hasten haematological recovery and to lower the risk of haemorrhagic complications.

Available data indicate that unrelated cord blood transplant (UCBT) is a suitable option for children with JMML lacking an HLA-compatible relative and that the search for an unrelated CB unit should be initiated at the same time as that for an unrelated BM donor (5). CB offers the advantage of prompt availability of stem cells and HSCT can be successful even in the presence of donor HLA disparities.

For children with JMML experiencing leukaemia relapse after allogeneic HSCT, DLI was proved to be largely ineffective (8), while a second allograft, from either the same or a different donor, together with reduction of the intensity of GvHD prophylaxis aimed at optimizing the GvL effect, is able to rescue about one third of the patients (9).

## 2.2. Other types of MDS

Data on outcome of HSCT in children with advanced MDS other than JMML are scanty, the reported disease-free survival (DFS) being in the order of 60% when the donor is an HLA identical sibling (10). The need for pre-HSCT remission induction chemotherapy remains a debated question in paediatric patients with RAEB and RAEB-t. In fact, it remains controversial whether cytoreductive therapy prior to HSCT for more advanced forms of MDS improves survival. A study published by the Nordic Pediatric Haematology group, comparing the outcome of children with *de novo* MDS (including JMML) and children with *de novo* AML, documented that patients belonging to the former group had a lower rate of complete remission and a higher risk of death for treatment-related complications (11). In an EWOG-MDS analysis

on children with MDS other than JMML, the outcome of patients given intensive chemotherapy prior to the allograft was found to be absolutely comparable to that of children who were transplanted directly (12).

Patients with RC must be considered for an early allograft from either a related or an unrelated donor if they have cytogenetic abnormalities, in particular monosomy 7. In fact, a study of the EWOG-MDS analysing children with RC has clearly demonstrated that the probability of progression to more advanced MDS (i.e. RAEB and RAEB-t), as well as to frank AML, is significantly higher in patients with monosomy 7 than in those with a normal karyotype (6). Moreover, this study has also shown that patients who had not progressed to advanced MDS prior to HSCT had a significantly better probability of survival than patients who experienced disease progression (76 versus 36%, respectively,  $p=0.03$ ) (6). In the presence of a normal karyotype, a substantial proportion of children with RC may experience a long, stable course of their disease. In view of the low TRM observed in patients transplanted from an HLA-compatible sibling, HSCT may be recommended if a suitable HLA-matched relative is available. A "watch and wait" approach with careful observation may be reasonable for patients without an HLA-identical sibling in the absence of transfusion requirements, severe cytopenia or infections.

As the risk of disease recurrence after the allograft in patients with RC is low, there is a great interest in testing the safety and efficacy of reduced intensity regimens in this setting. In a recent EWOG-MDS report, patients with RC and normal karyotype transplanted from an unrelated donor following a fludarabine-based reduced-intensity regimen had a favourable post-transplant outcome, which was comparable to that obtained in patients transplanted following a myeloablative conditioning regimen (13).

The outcome of children with MDS secondary to previous cytotoxic or radiant treatment remains still poor, for both a high risk of disease recurrence and TRM. Only one study proposed by the Children Cancer Group, which enrolled a limited number of children, has addressed the issue of autologous HSCT in childhood MDS. In this trial, children lacking an HLA-compatible sibling received intensively timed induction therapy, which was followed by 4-hydroperoxycyclophosphamide-purged autologous marrow transplantation (14). Further larger studies are needed before recommending autologous transplantation in children with MDS other than JMML lacking a suitable compatible donor.

### 3. Conclusions and future perspectives

The available data indicate that HSCT is curative for the majority of children with MDS, the outcome of patients transplanted from either an HLA-identical sibling or

an unrelated volunteer being comparable in more recent years. Strategies to reduce the risk of leukaemia recurrence in children with JMML, RAEB, RAEB-t and MDS secondary to previous treatment, as well as to abate TRM in children with RC, could further optimise the results of HSCT in childhood MDS.

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## Multiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/ebmt-handbook2008answers.htm>

1. **What is the percentage of children with JMML estimated to be cured with allogeneic HSCT?**
  - a) 25% .....
  - b) 75% .....
  - c) 90% .....
  - d) 50% .....
  
2. **Which is the most important prognostic factor predicting poor outcome for children with JMML given allogeneic HSCT?**
  - a) An age greater than 4 years at diagnosis .....
  - b) A monocyte count above  $3 \times 10^9/L$  .....
  - c) A leukocyte count above  $30 \times 10^9/L$  .....
  - d) Monosomy 7 .....
  
3. **Which is the best treatment for children with JMML relapsing after allogeneic HSCT?**
  - a) Single donor leukocyte infusion .....
  - b) Repeated donor leukocyte infusions .....
  - c) Second allogeneic HSCT .....
  - d) AML-like chemotherapy .....

**4. The risk of disease recurrence in children with refractory cytopenia is:**

- a) 30% . . . . .
- b) No more than 10% even with reduced intensity regimens . . . . .
- c) No more than 10% with myeloablative regimens, but much higher  
in patients given reduced intensity regimens . . . . .
- d) 50% . . . . .

**5. In children with advanced MDS (i.e. RAEB and RAEB-t):**

- a) Pre-HSCT remission induction chemotherapy should always  
be employed . . . . .
- b) Pre-HSCT remission induction chemotherapy should never  
be employed . . . . .
- c) Pre-HSCT remission induction chemotherapy remains  
a debated question . . . . .
- d) Pre-HSCT remission induction chemotherapy should always  
be employed above 10% bone marrow blasts . . . . .

## NOTES