

* CHAPTER 35

HSCT for acute myeloid leukaemia in children

G. Dini, M. Miano

1. Introduction

The prognosis of acute myeloid leukaemia (AML) in children has significantly improved over the past two decades: with intensive chemotherapy 80–90% of children achieve complete remission (CR) and 30–70% are cured if they receive post-induction chemotherapy (1). Matched related donor (MRD) transplantation in first CR results in 45–64% long-term survival and represents an attractive option for children with high risk (HR) AML (2). However, since approximately 60% of children lack an MRD, the pros and cons of alternative approaches must be carefully weighed on a case-by-case basis.

2. Indications

Recently, the European Group for Blood and Marrow Transplantation (EBMT) published indications for HSCT in all diseases, including AML. These are shown in Table 1 (3).

Table 1: Indications for HSCT for children with acute myeloid leukaemia

Disease	Status	Sibling donor	Well matched unrelated / 1 Ag related	Mm unrelated / >1 Ag related	Auto-HSCT
AML	CR1 low-risk	GNR	GNR	GNR	GNR
	CR1 high-risk	S	CO	GNR	S
	CR1 very high-risk	S	S	CO	GNR
	CR2	S	S	S	S
	>CR2	CO	D	D	GNR

S: standard of care; generally indicated in suitable patients. CO: clinical option; can be carried out after careful assessment of risks and benefits. D: developmental; further trials are needed. GNR: generally not recommended. NA: not applicable. CR1, 2: first, second complete remission. Ag: antigen. Mm: mismatched. This classification does not cover patients for whom a syngeneic donor is available

3. Conditioning regimens

Total body irradiation (TBI) was found to have no favourable impact on event free survival (EFS) in children undergoing HSCT for 1st CR AML. Thus, given its deleterious effect of provoking late sequelae, radiotherapy should no longer be administered to this subset of patients. Most teams currently use non-TBI-containing regimens in children transplanted for AML. The most commonly used regimens include busulfan and cyclophosphamide, almost always supplemented with melphalan. Some teams still use fractionated TBI-containing regimens, especially in high-risk

cases (4). No studies comparing these two approaches in the treatment of paediatric AML have so far been published. However, the International-BFM-Study Group is comparing the two key preparative regimens (i.e., Bu+Cy+Mel vs. ftBI+Cy) as optional therapy in their ongoing trial on relapsed AML.

4. Role and outcome of autologous transplant

Autologous HSCT has been widely used as consolidation treatment after induction therapy in children with HR AML in first or second CR lacking an MRD. However, the results of paediatric studies comparing autologous HSCT to chemotherapy are conflicting. Further randomised clinical trials are needed to address the pivotal clinical question of whether auto-HSCT is better than chemotherapy or allograft as consolidation treatment for childhood AML in first CR.

A recent EBMT retrospective study involving 387 children given autologous HSCT for 1st CR AML showed that 5-year transplant related mortality (TRM), relapse rate (RR) and EFS were 3, 39 and 60%, respectively (5). A lower probability of survival was observed when; a) more than two induction courses were needed to reach CR, b) the median interval between diagnosis and achievement of CR was greater than 38 days, and c) the number of infused cells was above $2.85 \times 10^8/\text{kg}$. A trend towards a favourable effect of purging on the probability of EFS was observed. Children receiving BAVC as the conditioning regimen showed a higher relapse rate

4.1. Open questions and future directions

Use of peripheral blood progenitor cells

Peripheral blood progenitor cells (PBPCs) are not often used for autologous HSCT in children with AML. This is mainly due to the difficulty in collecting adequate numbers of circulating haematopoietic progenitor cells, not to mention the poorly defined effect that is observed in this subset of children when PBPCs are used to accelerate the recovery of haematopoiesis.

Role of haematopoietic growth factors

The beneficial impact of haematopoietic growth factors on myeloid recovery in children undergoing autologous HSCT for AML has not been proven, and given the cost of these cytokines, their use in this subset of patients should be avoided.

In vitro purging

In vitro purging is associated with reduced RR ($p=0.04$) (5). Delayed platelet engraftment is one of the drawbacks that may be observed. These data (5) suggest that *in vitro* purging should be used before carrying out autologous transplantation in childhood AML.

5. Role and outcome of HLA-identical sibling transplant

Several randomised trials have shown the statistically significant superiority of MRD HSCT as compared to all other options. This, in turn, is correlated with longer periods of “quality of life time” (2). In a recent, single-centre, retrospective study involving 55 children receiving MRD HSCT for 1st CR AML, the 5-year probability of survival was 74%, whereas the 5-year probability of relapse was 26% (6). None of the patients who developed acute graft versus host disease (GvHD) relapsed, confirming a graft versus leukaemia (GvL) effect following allogeneic HSCT for AML. Better EFS among the older children receiving a higher dose of TBI was observed in this study. This issue was recently confirmed by a review of the literature comparing various TBI regimens (7).

6. Role and outcome of Unrelated Donor (UD) transplant

There is an absolute indication for UD HSCT in infant AML and in children with FAB M7 AML, who stand a very poor chance of being cured by chemotherapy or by autologous HSCT. FAB M0 or M6 represent more controversial indications. Timing in the identification of a suitable donor constitutes a limiting factor for this subset of patients.

As compared to unrelated cord blood transplantation (UCBT), UD-HSCT has shown a similar incidence of grade III-IV acute GvHD and a higher incidence of chronic GvHD, while 2 year overall survival is similar (8).

A recent study from the USA has shown that the 5-year EFS of children given an 8/8 allele matched UD-HSCT is similar to results obtained with a 1 or 2 antigen mismatched UCBT. TRM is slightly higher and relapse rate is lower after a 2 antigen mismatched UCBT (9).

7. Role and outcome of cord blood transplant

Eurocord recently reported that the EFS of children with AML in 1st CR and in 2nd CR is 57 and 47%, respectively, while the RR is 10% in CR1 and 23% in CR2. The main prognostic factors are disease stage and number of infused cells (10).

8. Role and outcome of haploidentical transplants

The results reported by the Perugia Group regarding patients with AML undergoing haploidentical HSCT showed that NK cells have an impressive effect on alloreactivity. In fact, no relapses occurred among the patients transplanted from haploidentical donors with KIR mismatched in the GvL direction, suggesting that the haploidentical option may play a role in the early phase of treatment for very high-risk AML patients. *In vitro* studies have confirmed that alloreactive NK clones exert a potent cytotoxic

activity against the leukaemic cells taken from patients with CML and AML (11). More recently, several paediatric teams began to investigate the use of haploidentical HSCT in children with no other allogeneic donor options, or with an urgent need to proceed to transplant. Preliminary results confirm that the outcome of children in remission is similar to what can be achieved by using other donor stem cell sources (12).

9. Nature and role of Donor Lymphocyte Infusion

A multi-centre study in children with AML showed that despite early donor lymphocyte infusion (DLI), relapse was still significantly more frequent in patients with increasing mixed chimerism (MC) than it was in patients with complete chimerism (CC), low-level MC (i.e. low level of host cells) or decreasing MC. Patients with increasing MC who received early DLI showed a significantly higher probability of EFS than patients with increasing MC who did not undergo immunological intervention. These results demonstrate that paediatric AML patients with increasing MC are at highest risk of relapse, and that early DLI can prevent relapse in these patients (13).

10. A treatment algorithm

A suitably matched UD (8/8 or >/10 allele matched) can usually be located within 4 to 6 weeks for children with the most common haplotypes who lack an MRD. Alternative treatment options should be offered to children with rare HLA types, and a decision should be made as to whether to reduce the matching requirements or to select another type of therapy, such as UCBT or haploidentical HSCT. A matched or 1 antigen mismatched CB Unit containing more than 3×10^7 mononuclear cells should be considered equivalent to an 8/8 allele matched UD. The decision should be made based on the urgency of the HSCT. Haploidentical HSCT should be offered if no donors and no CB units with the above mentioned characteristics are available. Some teams consider haploidentical HSCT the second option when an acceptable unrelated donor is not available.

Acknowledgments

G. Dini thanks V. Perricone for revising the manuscript.

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Multiple Choice Questionnaire

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

1. The standard treatment for patients with high-risk AML in CR1 is:

- a) Allogeneic HSCT.....
- b) Autologous HSCT.....
- c) Chemotherapy.....
- d) Radiotherapy.....

2. The main risk factor for EFS in patients receiving allogeneic HSCT for AML is:

- a) Age.....
- b) LDH levels before HSCT.....
- c) FAB Classification.....
- d) WBC count.....

3. The standard treatment for patients suffering from low risk AML in CR1 is:

- a) Allogeneic HSCT.....
- b) Autologous HSCT.....
- c) Chemotherapy.....
- d) Radiotherapy.....

4. For patients with AML in CR2, which of the following criteria selects those who should receive allogeneic HSCT?

- a) Age.....
- b) LDH levels.....
- c) All patients represent an indication.....
- d) WBC number.....

5. Which of the following is true for allogeneic HSCT for patients suffering from AML in CR2?

- a) Generally indicated in suitable patients.....
- b) Not recommended.....

- c) A developmental option to be demonstrated with further trials
- d) Indicated after relapse following autologous HSCT