

## \* CHAPTER 38

# HSCT for chronic myeloproliferative disorders in children

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## 1. Introduction

Among chronic myeloproliferative disorders (MPD), CML certainly represents the most common variant, accounting for approximately 3–5% of all leukaemias in childhood (1). The estimated incidence of Philadelphia (Ph+) CML in paediatric patients has been reported to be less than 1 in 100,000 and it is less common under the age of 2 as compared with other age groups (2). In children, the disease is characterised by the same molecular, cytogenetic, clinical and morphological features reported in adults with classical CML.

As in adults, so far, allogeneic HSCT is considered to be the only proven curative treatment for children with Ph+ CML (3–6). However, it must be underlined that not all candidates for transplantation have a suitable donor, either related or unrelated, and, despite its curative potential, HSCT carries the risk of death associated with the procedure, as well as of leukaemia recurrence. Moreover, the natural history of Ph+ CML has been recently profoundly modified by the introduction of the specific Bcr/Abl tyrosine protein kinase inhibitors, the most frequently employed being imatinib mesylate, which target the enzymatic activity of the Bcr-Abl protein, occupying the ATP-binding pocket of the molecule. The tyrosine kinase inhibitors have a high probability of inducing the achievement of both major and complete cytogenetic response and a high rate of freedom from progression to AP or BC (7). So far, however, we do not have convincing evidence that the Ph+ clone can be either completely eradicated or rendered silent for many decades by prolonged treatment with tyrosine kinase inhibitors.

Other MPD, such as polycythaemia vera (PV) and myelofibrosis with myeloid metaplasia (MMM), are extremely rare in children and no sound data are available for analysing the role of HSCT in children affected by these disorders.

## 2. Indications, results and risk factors

In some of the most important studies addressing the role of HSCT in patients with Ph+ CML, children have been included in adult series, but they represented a small proportion of the patient group and their outcome was not considered separately (3–5). Recently, the Chronic Leukemia Registry of the European Group for Blood and Marrow Transplantation (EBMT) has evaluated the outcome of 314 children with CML transplanted between 1985 and 2001 from either a related donor or an unrelated one, selected using high-resolution molecular typing of HLA class II antigens only (6). In this study, 3-year OS and LFS were 66 and 55%, respectively. In multivariate analysis for both OS and LFS, outcome was superior in patients given the allograft in CP1 versus advanced phase, although it is noteworthy that more than one third of patients transplanted in AP or BC are alive and disease free 3 years after

transplantation (6). Inferior LFS was also found in children transplanted more than 6 months from diagnosis, this finding confirming previously published studies, which documented a worse outcome for adult patients transplanted more than 12 months after diagnosis as compared to those given HSCT earlier. The TRM in the cohort of patients analysed by the EBMT group was significantly higher for children transplanted from an unrelated volunteer donor, these patients having a 35% chance of fatal transplantation-related complications as compared to 20% for recipients of sibling allografts (6). The higher incidence of transplant-related death observed in patients transplanted from an unrelated volunteer is mainly due to a greater incidence of severe GvHD in these recipients as compared to those transplanted from an HLA-compatible sibling. A more precise characterisation of HLA alleles using high-resolution typing for both Class I and Class II molecules may permit a more accurate selection of unrelated donors, thus reducing the incidence of immune-mediated complications and fatal events after the allograft (8, 9). Thus, for patients transplanted in more recent years, the outcome of patients given HSCT from an unrelated volunteer is comparable to that of patients transplanted from a compatible sibling.

Treatment of CML relapse after an allograft has significantly benefited from adoptive immunotherapy with DLI. In fact, in patients with CML experiencing haematological relapse in CP after HSCT, complete remission can be obtained with this treatment in approximately 70% of cases (10). Most of these remissions are sustained over time, this proving the capacity of DLI to eradicate clonogenic leukaemia cells or to control their re-growth. Patients suffering from either cytogenetic or molecular relapse have an even greater chance of benefiting from DLI than those experiencing haematological relapse, especially if in advanced phase.

### 3. Conclusions and future perspectives

The available data indicate that HSCT is curative for the majority of children with CML, although in the past TRM unfavourably affected the outcome of patients transplanted from an unrelated volunteer donor. Long-term survival is also influenced by the stage of the disease at time of transplantation, significantly better outcome having been observed in patients transplanted in CP1. This observation, together with the finding that LFS is significantly better for children transplanted within 6 months of diagnosis, suggests that it is important to proceed to HSCT as soon as an HLA-identical donor has been identified. It is possible that in the future the choice of transplanting children with CML will have to be balanced against the results achieved with tyrosine kinase inhibitors. However, considering the long life expectancy of children, if these agents do not prove to be able to offer, either alone

or in combination with other treatment, a sustained “molecular cure” or indefinitely prolonged CP of the disease, HSCT, possibly in the first year after diagnosis, remains the treatment of choice of childhood Ph+ CML, provided that a well-matched donor is available.

Strict monitoring and early detection of minimal residual disease through serial quantitative evaluation of the chimaeric Bcr/Abl mRNA transcript by means of PCR can be extremely useful for ensuring the best chance of favourable outcome in patients with Ph+ CML given HSCT.

## References

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## Mutiple Choice Questionnaire

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

### 1. What is the estimated incidence of Philadelphia (Ph+) CML in paediatric patients?

- a) Less than 1 in 100,000 .....
- b) Less than 1 in 1,000,000 .....
- c) 1 in 50,000 .....
- d) 1 in 10,000 .....

### 2. Which is the most important prognostic factor predicting poor outcome for children with Ph+ CML given allogeneic HSCT?

- a) To have been splenectomised before transplantation .....
- b) To be transplanted in accelerated phase, blast crisis or second chronic phase .....
- c) To have been treated with interferon before transplantation .....
- d) To be younger than 10 years at time of the allograft .....

### 3. Which is the best first-line treatment for children with Ph+ CML relapsing after allogeneic HSCT?

- a) Single or repeated donor leukocyte infusions .....
- b) Inhibitors of tyrosine kinase .....
- c) Second allogeneic HSCT .....
- d) Initial treatment with inhibitors of tyrosine kinase followed by single or repeated donor leukocyte infusions .....

### 4. Which is the most important cause of treatment failure in children with 1<sup>st</sup> chronic phase Ph+ CML?

- a) Relapse .....
- b) Treatment-related mortality .....
- c) Equally both relapse and treatment-related mortality .....
- d) Secondary malignancies .....

**5. Which is the chance of definitive cure with allogeneic HSCT in children with myelofibrosis and polycythaemia vera?**

- a) 90% .....
- b) 70% .....
- c) 50% .....
- d) No sound data are available for analysing the role of HSCT in children affected by these disorders. ....