

* CHAPTER 39

HSCT for lymphomas in children

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1. Introduction

The prognosis for children suffering from Hodgkin's disease (HD) and non Hodgkin's lymphoma (NHL) is good, even in patients with advanced disease (1–3). Patients who fail to respond to first line chemotherapy and radiotherapy, or who present with recurrent disease can achieve long-term, disease free survival (DFS) after autologous haematopoietic stem cell transplantation (HSCT) (4). This procedure has historically been preferred to allogeneic HSCT due to its greater availability and the absence of immunologic complications. Nevertheless, allogeneic HSCT has been attempted for the treatment of both diseases on a number of occasions, but data concerning paediatric settings are scarce. During the last few years, the high rate of transplant-related mortality (TRM), which is also due to the advanced disease status of the patients undergoing allogeneic HSCT, has limited the use of this procedure in these patients. New approaches have been developed and adopted to reduce TRM, including the use of reduced-intensity conditioning regimens, which rely on the potential graft-versus-lymphoma (GvL) effect rather than on the conditioning regimen itself.

2. Indications

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

3. Non-Hodgkin's lymphomas

3.1. Role and outcome of autologous and allogeneic HSCT

There are few published reports on exclusively paediatric populations suffering from NHL undergoing HSCT.

In a study of 46 paediatric patients (5), no differences were shown in terms of event free survival (EFS) (57%) between the groups of patients receiving autologous (32 pts) or allogeneic (14 pts) HSCT. Three out of 32 (9%) and 3/14 children (21%) undergoing autologous and allogeneic HSCT, respectively, died of transplant related toxicity.

Currently, the true impact of allogeneic HSCT in children with NHL remains to be clarified. One study of 10 children with poor prognosis NHL treated by allogeneic HSCT showed an overall survival (OS) probability of 56% at a median follow-up of 29 months (6). An EBMT retrospective study reported data on 136 children receiving allogeneic transplantation for NHL (7). At a median follow-up of 1.2 years, 51% of patients were alive. OS was influenced by status at HSCT. Thus, OS was 74% for patients transplanted in CR, and 56% for those with sensitive relapse while only

Table 1: Indications for HSCT in children with lymphoma

| Disease | Status | Sibling donor | Well matched unrelated / 1 Ag related | Mm unrelated / >1 Ag related | Auto-HSCT |
|---------|---------------|---------------|---------------------------------------|------------------------------|-----------|
| NHL | CR1 low-risk | GNR | GNR | GNR | GNR |
| | CR1 high-risk | CO | CO | GNR | CO |
| | CR2 | S | S | CO | CO |
| HD | CR1 | GNR | GNR | GNR | GNR |
| | Relapse, CR2 | CO | D | GNR | S |

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. CR1, 2: first, second complete remission. Ag: antigen. Mm: mismatched

27% with refractory disease survived. Relapse occurred in 21 of the 70 (30%) large B-cell lymphoma, but in only 4 of 28 (14%) anaplastic large cell lymphoma (ALCL) patients. ALCL represents a special category among NH lymphomas. A very low treatment failure rate (3 year EFS 75%, and TRM 15%) was observed in a series of 20 children suffering from relapsed ALCL that had been treated by allogeneic HSCT. The effectiveness of allogeneic HSCT, even in patients with chemotherapy-resistant or progressive disease suggests a role of graft vs. ALCL effect (8).

3.1.1. Risk factors

The only predictive factors for EFS are the type of lymphoma and the disease status at transplant, with significantly worse EFS being observed in patients with less favourable disease status.

4. Hodgkin's disease

4.1. Role and outcome of autologous HSCT

Children suffering from HD who are treated with chemotherapy alone or associated with radiotherapy currently have a 5-year DFS rate of over 85%. Patients who are resistant to first line therapy or who have recurrent disease need to undergo salvage treatment. In the adult setting, high-dose chemotherapy with autologous stem cell transplantation represents the standard treatment for this high-risk population. This approach is also frequently used in the paediatric population. A report of 53 children and adolescents undergoing autologous HSCT showed actuarial EFS of 31% and an OS of 43% (9).

The results of another retrospective study on 51 children showed no statistically significant differences in OS in patients who were treated with autologous HSCT or with conventional salvage therapy. Nonetheless, patients with resistant disease showed a significant survival advantage with HSCT (10). Overall, these results justify the use of autologous HSCT as a primary therapeutic option for patients with resistant or relapsing disease.

4.1.1. Risk factors

Pre-transplantation LDH levels represent an important prognostic factor for 5-year EFS: 42 vs. 0% for patients with normal or high levels, respectively. Pre-transplant positive positron emission tomography proved to be an indicator of poor prognosis in a large group of patients that included children (11).

4.2. Role and outcome of allogeneic HSCT

Few data are currently available regarding the outcome of allogeneic HSCT in children with Hodgkin's disease. All available data refer to adult populations. Increasing evidence supporting the concept of a GvL effect, as well as the gradual improvement in both TRM rates and in the non-myeloablative conditioning regimens support the idea that the role of allogeneic HSCT should be re-evaluated.

5. Conclusions

Autologous HSCT represents a valid treatment option for patients suffering from lymphomas after relapse, or for those with resistant disease. The true impact of allogeneic transplantation has not yet been clarified. The gradual improvement in TRM together with the possibility of administering a reduced intensity conditioning regimen should lead to a re-evaluation of the use of allogeneic HSCT for high-risk children. Novel imaging and molecular techniques should be further investigated to better identify high-risk groups of patients who need more intensive treatment.

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Mutiple Choice Questionnaire

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

1. The standard treatment for patients suffering from HL with responding relapsed disease is:

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

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

- a) LDH levels before HSCT

- b) Disease status
- c) Histology
- d) WBC count

3. The standard treatment for patients suffering from low risk NHL in 1st CR is:

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

4. The main risk factor for patients receiving autologous HSCT for Hodgkin's lymphoma is:

- a) LDH levels before HSCT
- b) Disease status
- c) Histology
- d) WBC count

5. Which of the following is true of allogeneic HSCT for patients suffering from relapsed NHL:

- a) Generally indicated in suitable patients
- b) A clinical option that can be carried out after careful assessment of risks and benefits
- c) Is not recommended
- d) Indicated after relapse following autologous HSCT