

## \* CHAPTER 28

# HSCT for high-grade non-Hodgkin's lymphoma in adults

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## 1. Introduction

This review will discuss the indications, role and outcome of haematopoietic stem cell transplantation in patients with aggressive non-Hodgkin's lymphoma (NHL). The specific disease entities which we will consider are diffuse large B-cell lymphoma (DLBCL) and peripheral T-cell lymphoma (PTCL).

The outcome of patients with high-intermediate and high-risk aggressive NHL is unsatisfactory with standard treatment approaches. In DLBCL approximately half of patients with high-intermediate and high-risk disease are cured with immunochemotherapy, usually R-CHOP, but the results are worse for patients with PTCL. Thus these patients may be candidates for front-line high-dose therapy (HDT) and autologous stem cell transplantation (ASCT). In younger patients with relapsed or refractory chemosensitive aggressive lymphoma HDT can be curative in a significant subset. However, many areas of uncertainty remain, such as the effectiveness of these strategies in patients with DLBCL who receive new standard therapies containing rituximab and the role of allogeneic transplantation in aggressive NHL.

## 2. High-dose therapy and autologous stem cell transplantation in first-line therapy of aggressive non-Hodgkin's lymphoma

HDT has been used as part of front-line therapy in an effort to improve results in young patients with aggressive NHL. Comparison between the various trials is difficult due to the inclusion of disparate patient groups (in terms of definition of risk, remission status and histology) and different therapeutic strategies in the transplantation and standard therapy arms.

Four randomised trials have demonstrated a benefit of this approach in terms of an improvement in event-free survival (EFS) or overall survival (OS) in patients less than 60 years with aggressive NHL and high-risk features (e.g. age-adjusted International Prognostic Index (aaIPI) score of 2 or 3). All these studies included DLBCL and PTCL and were carried out before the era of monoclonal antibodies. For example, the LNH 87-2 trial randomised 236 patients with aaIPI of 2 or 3 who achieved complete remission (CR) after induction therapy to HDT or sequential consolidation and found a 8-year OS rate of 64% in the HDT arm compared with 49% in the sequential chemotherapy arm ( $p=0.04$ ).

However, a number of other trials, including the GELA trial LNH 93-3, the study of the German High-Grade NHL Study Group and the EORTC study, have not demonstrated a benefit of this approach in front-line therapy. Many, but not all, of the negative trials have utilised an abbreviated induction regime in the transplant arm, suggesting they may not have had adequate dose-intensity before HDT. The majority of patients in the EORTC trial belonged to favourable IPI risk groups. A multicentre European

study (MISTRAL study) which compared 6–8 cycles of CHOP-21 with sequential HDT found no benefit and increased toxicity in the sequential HDT arm.

A recent meta-analysis of 15 randomised trials was not conclusive but suggested a benefit of front-line HDT in poor risk patients with aggressive lymphoma (1).

Immunochemotherapy with rituximab is now considered the standard of care in DLBCL. No randomised comparison exists of HDT after immunochemotherapy with rituximab in DLBCL. The results of trials that evaluate the relevance of this approach in the rituximab era are eagerly awaited.

The role of HDT as consolidation therapy for patients with PTCL in first CR has not been defined. The majority of studies in this area are small, retrospective and heterogeneous. Some are confounded by the inclusion of patients with ALK-positive anaplastic large cell lymphoma which has a favourable prognosis when treated with chemotherapy alone. In subgroup analyses of PTCL included in the two GELA studies that examined this approach, there did not appear to be a benefit of HDT/ASCT over sequential chemotherapy for these patients (2, 3). A number of other retrospective analyses suggest a benefit of HDT over conventional chemotherapy. In a prospective study currently ongoing, a significant minority of patients (28%) were not transplanted due to early progression before myeloablative therapy (4). Due to the very poor prognosis of these patients with conventional chemotherapy, further prospective studies of the potential benefit of early HDT are needed.

### **3. High-dose therapy and autologous stem cell transplant in relapsed and refractory aggressive non-Hodgkin's lymphoma**

The PARMA study established HDT as the standard of care in patients with chemosensitive relapsed aggressive NHL. In this study, 109 patients who demonstrated responsiveness to salvage chemotherapy with DHAP were randomly assigned to receive four further cycles of DHAP or intensive chemotherapy. Survival at five years was superior in the transplantation arm compared to the conventional chemotherapy arm, 53 versus 32% ( $p=0.038$ ). Subsequent analyses of this cohort have demonstrated that time to relapse, less than 12 months versus greater than 12 months, was the most important prognostic factor influencing OS after relapse. At 8 years 13% of patients who relapsed early were projected to be alive compared with 29% of those who relapsed late ( $p<0.00001$ ). The second-line aaIPI as well as the quality of response to salvage chemotherapy (CR versus PR) have also been demonstrated to be important prognostic factors in patients with relapsed and refractory aggressive lymphoma. A number of studies have demonstrated a similar benefit of HDT in patients with primary refractory aggressive lymphoma compared to those with relapsed disease, provided they remain chemosensitive (5). By contrast, patients with chemotherapy

resistance do very poorly with HDT with long-term EFS in the order of 10% or less and thus are not considered candidates for this therapy.

The prognosis of transformed low-grade B-cell lymphomas is generally poor. Although the data on HDT in this setting is limited and retrospective, it appears that approximately one-third of patients remain disease-free at five years (6). Thus it should be considered in eligible patients with chemosensitive disease.

Available evidence suggests that patients with chemosensitive relapsed and refractory PTCL have similar outcomes with HDT to patients with relapsed aggressive B-cell lymphoma, despite the fact that the T-cell phenotype is demonstrated to be an adverse prognostic factor for primary therapy (7). However this is unlikely to hold true with the addition of rituximab to salvage chemotherapy and transplant protocols for DLBCL.

As discussed above, the quality of the response to salvage therapy is an important prognostic factor, thus attempts have been made to improve results of ASCT by increasing the rate of CR to salvage therapy. The benefit of the addition of rituximab to salvage chemotherapy in DLBCL has been confirmed in a recent randomised trial of the HOVON group which compared salvage treatment with DHAP to that with R-DHAP and found a significant advantage in terms of failure-free and OS (8). It is currently unknown which salvage protocol is the most efficacious. The ongoing Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) trial compares R-DHAP and R-ICE as salvage regimens prior to HDT and aims to answer this question in patients with relapsed DLBCL. A second randomisation looks at the role of rituximab maintenance therapy in these patients.

Other strategies to improve the outcome of these patients are currently being explored. In DLBCL the addition of rituximab to pre- and post-transplantation therapy appears to be feasible and a phase III Intergroup trial is currently evaluating this approach. The incorporation of radioimmunoconjugates targeting the CD20 antigen in DLBCL is another promising approach under evaluation.

#### **4. Allogeneic stem cell transplantation and aggressive non-Hodgkin's lymphoma**

The role of allogeneic transplantation in aggressive NHL is uncertain. Theoretical advantages over autologous stem cell transplantation include a pure stem cell source free of tumour contamination and the possibility of a graft-versus-lymphoma effect. High treatment-related mortality of conventional myeloablative allogeneic transplantation (33% for high-grade lymphoma in an EBMT registry study) has hindered further development of this modality (9). Reduced-intensity conditioning (RIC) approaches can reduce treatment-related mortality but rely on a graft-versus-

lymphoma effect. The evidence for a significant graft-versus-lymphoma effect in DLBCL is lacking. There are few data available on the role of allogeneic stem cell transplantation in PTCL. A small prospective series of RIC allogeneic transplant in relapsed or refractory PTCL suggested the existence of a graft-versus-T-cell lymphoma effect with promising 3-year OS rates. Further studies of this approach in this poor-prognosis group are warranted. In certain subtypes of PTCL with an abysmal prognosis (e.g. hepatosplenic T-cell lymphoma) allogeneic stem cell transplantation may be considered to consolidate first-line therapy. There are reports of long-term disease-free survival after allogeneic transplantation in patients with chemorefractory aggressive NHL (10), thus this approach may be considered in suitable patients with aggressive NHL not responding to salvage chemotherapy.

## 5. Conclusions

HDT may have a role in improving the prognosis of young patients with poor risk aggressive lymphoma in front-line therapy and prospective randomised studies comparing HDT to new rituximab-containing standard therapies in DLBCL are needed. In PTCL prospective randomised trials are required to evaluate the benefit of HDT in the front-line setting and this will require international collaboration. Where possible these high-risk patients should be enrolled in clinical trials.

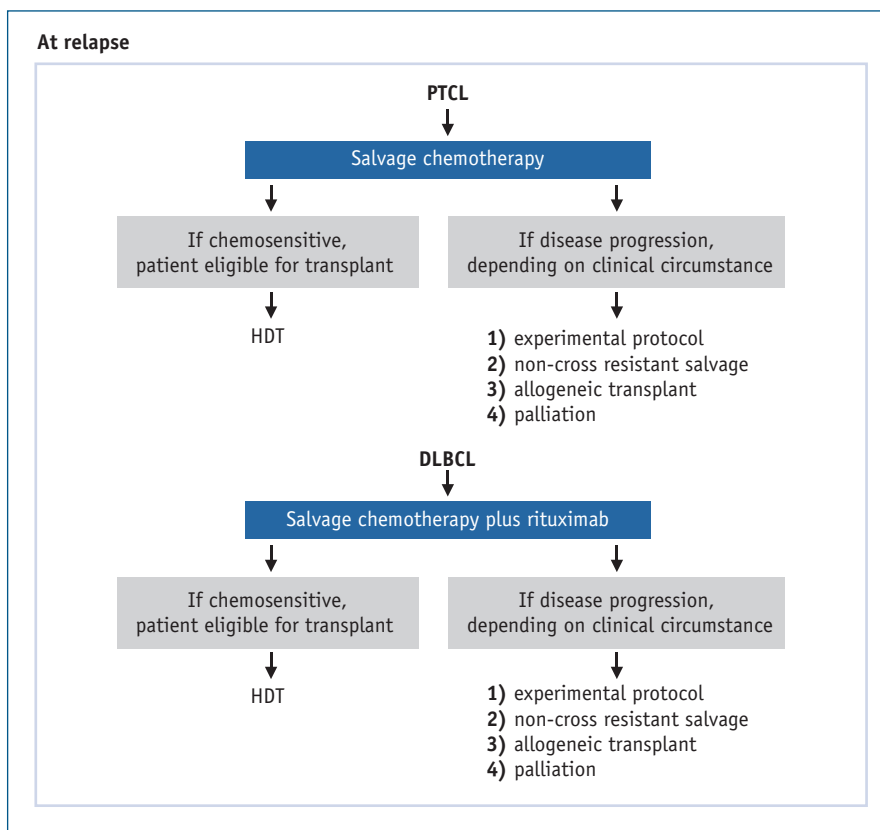
In patients with relapsed and refractory chemosensitive aggressive lymphoma HDT is demonstrated to improve outcome compared to conventional chemotherapy. Current efforts are focused upon identifying the optimal salvage regimen, defining the role of rituximab pre- and post-ASCT and optimally incorporating radioimmunoconjugates in transplant protocols (Figure 1).

**Figure 1: Summary algorithm for treatment of aggressive NHL**

### At diagnosis

- |              |   |  |
|--------------|---|--|
| <b>PTCL</b>  | → | <ol style="list-style-type: none"> <li>1) Enrol in clinical trial if possible</li> <li>2) If no clinical trial available consider HDT as consolidation in young transplant eligible patient with high-risk features (e.g. aaIPI 2 or 3) and chemosensitive disease (except ALK-positive ALCL)</li> </ol>                       |
| <b>DLBCL</b> | → | <p>In young patient (<math>\leq 60</math> years) eligible for transplant with 2-3 factors of aaIPI;</p> <ol style="list-style-type: none"> <li>1) Enrol in clinical trial if possible</li> <li>2) If no clinical trial, consider HDT in patients with chemosensitive disease after discussion of risks and benefits</li> </ol> |

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## Multiple Choice Questionnaire

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

### 1. For which of these patients has high-dose therapy followed by autologous transplant been proven to increase the PFS?

- a) Patient 45 years old with peripheral T-cell lymphoma in CR after first line of chemotherapy .....
- b) Patient 45 years old with diffuse large B-cell lymphoma in PR after first line of chemotherapy .....
- c) Patient 45 years old with diffuse large B-cell lymphoma, IPI score of 1, in CR after first line of chemotherapy .....
- d) Patient 45 years old with diffuse large B-cell lymphoma, IPI score of 4, in CR after first line of chemotherapy .....

### 2. Which one of these propositions is *not* true?

- a) High-dose therapy followed by autologous transplant is the standard treatment for a young patient with a positive PET scan after 6 cycles of R-CHOP .....
- b) The efficacy of R-CHOP in patient with diffuse large B-cell

- lymphoma has decreased the indications of high-dose therapy with autologous transplant .....
- c) The best treatment for a relapsing patient with diffuse large B-cell lymphoma responding to salvage chemotherapy is high-dose therapy with autologous transplant .....
- d) A patient with diffuse large B-cell lymphoma in partial response may be treated with rituximab maintenance with same benefit and less toxicity than high-dose therapy with autologous transplant .....
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- 3. Which salvage regimen has been proven to be the best before high-dose therapy with autologous transplant in a patient with diffuse large B-cell lymphoma in first relapse?**
- a) ESHAP combined with rituximab .....
- b) DHAP combined with rituximab .....
- c) ICE combined with rituximab .....
- d) All three of them .....
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- 4. What is the best strategy for a patient aged 45 years who progressed during treatment with R-CHOP?**
- a) Salvage with another chemotherapy regimen combined with rituximab ...
- b) Salvage with another chemotherapy regimen combined with rituximab followed by autologous transplant .....
- c) Salvage with another chemotherapy regimen combined with rituximab followed by an allogeneic transplant .....
- d) There is no good strategy .....
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- 5. Which one of these propositions is *not* true?**
- a) A combination of zevalin plus BEAM has not yet proven its efficacy compare to BEAM alone .....
- b) Outcome of a patient treated with high-dose therapy with autologous transplant is better if the patient reached CR with salvage regimen .....
- c) Outcome of a patient treated with high-dose therapy with autologous transplant is better if the patient relapsed more than 12 months after the first line treatment .....
- d) Other anti-CD20 monoclonal antibodies may replace rituximab with the same efficacy .....