SPECIAL ARTICLE

International Consensus Conference on High-Dose Therapy With Hematopoietic Stem Cell Transplantation in Aggressive Non-Hodgkin's Lymphomas: Report of the Jury

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IN THE SUMMER OF 1993, the first International Consensus Conference on Intensive Chemotherapy Plus Hematopoietic Stem Cell Transplantation in Malignancies was held in Lyon, France.[1] At that time, there were insufficient data to determine whether high-dose chemotherapy with autologous stem-cell support was "either superior or significantly worse than conventional combination chemotherapy in any stage of non-Hodgkin's lymphoma."[1] In the intervening years, a number of randomized studies have been completed that address important questions regarding the role of high-dose therapy with stem-cell support (HDT) in the aggressive non-Hodgkin's lymphomas (NHLs). For this reason, the original consensus conference organizers convened a second International Consensus Conference on High-Dose Therapy with Hematopoietic Stem Cell Transplantation in Aggressive Non-Hodgkin's Lymphomas in April 1998 and charged a jury with the task of evaluating available data on when and how to perform HDT in these diseases (Table 1). The jury operated under standard consensus conference guidelines. For each question regarding HDT in aggressive NHLs, the jury made a positive or negative recommendation or indicated that there were insufficient data to make a recommendation (Table 1). The quality of the evidence supporting each recommendation was also evaluated according to standard accepted criteria (Table 2).[2]

WHEN TO TRANSPLANT?

First or Subsequent Relapse

Chemosensitive relapse. The jury was first asked to identify settings in which high-dose therapy with hematopoietic stem cell support was the recommended treatment option (Table 1). Patients with chemosensitive first or subsequent relapses were thought to be appropriate candidates for HDT on the basis of the randomized prospective PARMA study (level 1 evidence [Table 2]).[3,4] In this study, 109 patients with chemosensitive first or subsequent relapse who received consolidative HDT were more likely to remain disease-free than patients who were given additional conventional salvage therapy (5-year event-free survival rates, 46% for HDT *v* 12% for conventional therapy, $P = .001$).[3] Further analysis of the PARMA study suggested that patients who relapsed within 12 months of their initial diagnosis were less likely to benefit from HDT than patients who relapsed at later time points. In PARMA study patients, the age-adjusted International Prognostic Index (IPI) at relapse was also predictive for long-term outcome. Although patients with an IPI score of 0 at relapse had comparable outcomes with HDT or conventional therapy, patients with IPI scores of 1 to 3 at relapse were more likely to remain disease-free if they received consolidative HDT. The jury noted that the PARMA study included only those patients with good performance status and no bone marrow involvement.[3] However, committee members believed that registry data (level 2 evidence [Table 2]) also supported the use of HDT in chemosensitive patients with marrow involvement or poor performance status at first or subsequent relapse (Table 1).

Untested relapse. The jury next addressed the question of whether patients in first or subsequent relapse should receive additional conventional salvage therapy before HDT or proceed directly to HDT in untested relapse (Table 1). In the jury's opinion, the recently completed randomized prospective LNH-93-RP study (level 1 evidence) supported the use of additional salvage chemotherapy before HDT.[5] In the LNH-93-RP study, patients who received additional salvage therapy before HDT had more favorable overall survival rates than those who proceeded to HDT in untested relapse (overall survival rates, 38% for salvage therapy *v* 21% for untested relapse, $P = .00085$).[5]

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Table 1. When and How To Perform HDT

	Consensus Recommendation	Evidence Quality (1 to 4)	Ref
When to transplant			
Is HDT appropriate in the treatment of:			
First or subsequent relapse?			
Chemosensitive relapse?	Yes (BM−)	1	3
	Yes (BM+)	2	
Untested relapse?	No	1	5
Chemorefractory relapse?	No	3	
Primary refractory disease (induction failure)	Yes	2	7
Is HDT appropriate as:			
Front line therapy?	Unknown	4	9-13
In selected patients?	Unknown	4	9-13
Which selection criteria should be used to identify appropriate patients for front-line HDT trials?			
Age-adjusted IPI	Yes	1-2	9-11
High risk only?	No	1-2	9-11
High-intermediate/high risk?	Yes	1-2	9-11
Low-intermediate?	No	1-2	9-11
Other available selection criteria?	Unknown	4	9-11
Therapy for slow or incomplete responders to standard induction therapy?	Unknown	4	14-15
How to transplant			
Is there a superior high-dose regimen?	No	2	
Single- versus repetitive-dose regimen?	Unknown	4	
Has a TBI-containing regimen been shown to be superior?	No	2	
Is there a preferred type of hematopoietic stem cell support?			
Autologous?	Yes	1	17-21
Allogeneic?	No	4	
Bone marrow?	No	1	17-20
PBSC?	Yes	1	17-20
Mobilized PBSC?	Yes	1	17-20
Umbilical cord stem cells?	Unknown	4	
Are there preferred forms of stem cell mobilization?			
Chemotherapy alone?	No	2	
Chemotherapy/cytokines?	Yes	2	
Cytokines alone?	No	3	
Are there specific clinical settings which warrant individual approaches to stem cell mobilization?	Yes	3	
Is there a role for a supplemental marrow?	No*	3	
Is there a demonstrated role for purging of autologous bone marrow or PBSC products?	No	4	
Positive selection	Unknown	4	
Is the patient with chemosensitive marrow involvement			
A transplant candidate?	Yes	2	
An autologous transplant candidate?	Yes	2	
An allogeneic transplant candidate?	Unknown	4	
A PBSC transplant candidate?	Yes	2	
Is an available matched sibling allogeneic transplant appropriate for:			
Patients with recurrent disease after autologous transplantation?	Unknown	4	
Is time to relapse relevant?	Unknown	4	
Relapsed young patients?	Unknown	4	

Abbreviations: BM, bone marrow; IPI, International Prognostic Index; PBSC, peripheral blood stem cells; TBI, total body irradiation.
*Certain individualized settings only.

Table 2. Quality of Evidence

1	Evidence obtained from at least one properly randomized controlled trial
2-1	Evidence obtained from well-designated, controlled trials without randomization
2-2	Evidence obtained from well-designated, cohort or case-controlled analytic studies, preferably from more than one center or research group
2-3	Evidence obtained from multiple timed series with or without the intervention, or from dramatic results in uncontrolled experiments
3	Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
4	Evidence inadequate owing to problems of methodology, eg, sample size, length or comprehensiveness of follow-up, or conflict in evidence

NOTE. Modified with permission from Stevens and Raftery.[2]

Chemorefractory relapse and primary refractory disease. The appropriateness of HDT in patients with chemorefractory first or subsequent relapse or primary refractory disease was also assessed (Table 1).[4] Interpretation of the data from different studies on HDT in primary refractory disease and chemorefractory relapse is hampered by the lack of uniform criteria to define chemorefractory disease.[4,6,7] For operative purposes, chemorefractory relapse was defined as stable or progressive disease after two cycles of an aggressive salvage regimen, whereas primary refractory disease (induction failure) was defined as stable or progressive disease documented at restaging immediately after the completion of induction therapy. On the basis of their own clinical experience and earlier pilot studies[6] (level 3 evidence [Table 2]), committee members agreed that HDT was inappropriate in chemorefractory first or subsequent relapse. In contrast, registry data suggest that a small subset of patients with primary refractory disease may benefit from HDT (level 2 evidence).[7] However, the jury expressed concern regarding the definition of primary refractory disease in this retrospective registry analysis.[7]

Induction Therapy

Induction therapy for newly diagnosed "high-risk" disease. The jury next assessed data regarding the role of HDT in newly diagnosed patients who were less likely to be cured with standard combination chemotherapy.[8] In trials completed to date, these "poor-prognosis" patients were identified using a variety of clinical parameters.[8] Several recent randomized prospective trials have compared upfront HDT to conventional induction therapy in poor-prognosis patients. However, these studies differed in both their design and conclusions. These differences in trial design and conclusions led the jury to characterize existing data as conflicting level 4 evidence (Table 2) and to recommend additional definitive studies.

Currently available randomized phase III studies of HDT in newly diagnosed high-risk patients include the LNH-87 trial,[9] the Italian Non-Hodgkin's Lymphoma Study Group trial,[10] the LNH-93 trial,[11] the German High-Grade Lymphoma Study Group trial,[12] and the Milan trial.[13] In these studies, the role of HDT was assessed after full-course standard induction therapy or abbreviated standard induction therapy or as upfront induction therapy.

HDT after full-course standard induction therapy. The LNH-87 study is one of the largest randomized prospective trials reported to date. In this study, 542 patients who were less than 55 years of age with at least one adverse prognostic factor and a complete response to full-course standard induction therapy were randomized to receive additional high-dose therapy and autologous bone marrow transplantation or additional conventional dose therapy.[9,14] In the initial analysis of all study patients, there were no treatment-related differences in 3-year overall survival (56% 3-year disease-free survival rate for both treatment arms).[14] However, treatment-related differences became apparent when study patients were retrospectively grouped into low, low-intermediate, and high-intermediate/high-risk groups according to the age-adjusted IPI.[9,14] In the updated analysis of patients followed for a median period of 53 months, low-risk and low-intermediate risk patients had similar outcomes when treated with either of the two regimens.[9] In contrast, high-intermediate/high-risk patients had increased disease-free and overall survival rates when they were treated with the high-dose experimental regimen (5-year disease-free survival rate, experimental *v* standard therapy, 57% *v* 36%, $P = .01$; 5-year overall survival, experimental *v* standard therapy, 65% *v* 52%, $P = .06$).[9]

The Italian Non-Hodgkin's Lymphoma Study Group trial included 124 patients less than 60 years of age with bulky (tumor > 10 cm) stage II or stage III/IV disease. Patients were randomized at study entry to receive standard induction therapy alone or the same regimen followed by autologous bone marrow transplantation (ABMT).[10] Patients who were randomized to receive standard induction therapy and achieved a complete response were simply followed; patients who obtained a partial response or no response or relapsed underwent conventional salvage therapy.[10] Patients randomized to standard induction therapy and ABMT were restaged after their initial induction therapy; however, complete, partial, and non-responders proceeded to ABMT. With a median follow-up of 42 months, the 6-year overall survival rates were identical (65%) in the two treatment arms.[10] However, when outcome was analyzed on the basis of age-adjusted IPI at diagnosis, patients with high-intermediate or high-risk disease were more likely to remain disease-free if they received additional high-dose therapy (3-year disease-free survival rate, 87% for HDT *v* 48% for standard therapy, $P = .008$).[10]

Retrospective analyses of the LNH-87 and Italian study group trials seem to support the use of consolidative HDT in high-intermediate or high-risk (IPI) patients who have completed standard-dose induction therapy. However, additional randomized trials in which patients received abbreviated standard induction therapy and subsequent HDT reach different conclusions.

HDT after abbreviated standard induction therapy. In the recently completed LNH-93 trial, 370 patients with high-intermediate and high-risk disease (according to the age-adjusted IPI) were randomized at diagnosis to receive standard induction therapy or three cycles of abbreviated induction therapy followed by HDT.[11] In the initial analyses of LNH-93, patients who underwent full-course conventional induction therapy actually had better outcomes than patients who received early HDT. With a median follow-up of 30 months, the event-free and overall survival rates for patients receiving full-course conventional induction therapy and early HDT were 54% and 63% (conventional induction therapy) *v* 41% and 47% (early HDT) ($P = .01$ and .003, respectively).[11]

In a similarly designed recent study, the German High-Grade Lymphoma Study Group randomized 312 patients who were less than 60 years of age with elevated lactate dehydrogenase levels to receive either five cycles of standard induction therapy or three cycles of standard induction therapy followed by HDT.[12] In initial analyses, the 2-year overall survival rates of patients in the two treatment arms were comparable.

Up-front high-dose induction therapy. Another experimental approach to the treatment of high-risk patients is to intensify their initial induction therapy.[13,15,16] In a recent study from Milan, 98 patients with bulky or advanced-stage disease were randomized at diagnosis to receive standard induction therapy or "high-dose sequential therapy" consisting of single-agent high-dose cyclophosphamide, methotrexate, and etoposide followed by melphalan/total body irradiation with bone marrow/peripheral blood stem-cell rescue.[13] In this small phase III study, patients who received high-dose sequential therapy had superior event-free survival rates (7-year event-free survival rates, 76% for high-dose sequential therapy *v* 49% for standard induction therapy, $P = .004$). However, overall survival rates were not significantly different in the two treatment groups (overall survival, 73% for high-dose sequential therapy *v* 62% for standard induction therapy, P = NS; median follow-up, 43 months) because of early treatment-related toxicity and the study's cross-over design.[13]

Comparison of the published phase III studies on HDT in newly diagnosed patients. It is of interest that the three "positive" randomized trials[9,10,13] included full-course standard induction therapy followed by HDT or upfront high-dose induction therapy, whereas the two "negative" studies[11,12] contained abbreviated (three-cycle) standard induction therapy and early HDT. In addition, the LNH-87 trial included only those patients who had achieved a complete response with standard induction therapy; in contrast, the LNH-93 trial, the Italian and German study group trials, and the Milan study included newly diagnosed untreated patients.

Additional ongoing studies. There are several ongoing randomized trials of HDT in newly diagnosed poor-prognosis patients with aggressive lymphoma. All of these studies use one of the above-mentioned treatment strategies. In the Swiss Group for Clinical and Epidemiological Cancer Research (SAKK) Mistral 2 and a European Organization for Research and Treatment of Cancer (EORTC) study, patients receive full-course induction therapy and undergo subsequent restaging. Responding patients are then randomized to undergo immediate HDT or HDT at relapse. In SAKK Mistral 1, patients are randomized at diagnosis to receive high-dose sequential therapy[13] or full-course standard induction therapy.

An additional United Kingdom Lymphoma Group (UKLG)/Australia–New Zealand (ANZ)/Nordic/European Bone Marrow Transplantation Group (EBMT) trial has an experimental design that is similar to that of the recently completed LNH-93[11] and German[12] studies. In the UKLG/ANZ/Nordic/EBMT study, patients are randomized at diagnosis to receive abbreviated standard induction therapy followed by HDT or full-course standard induction therapy.

The jury believed that these additional trials of HDT in newly diagnosed poor-prognosis patients will provide further insights regarding the benefits of this approach. Specifically, committee members believed that these studies will clarify the need for a prior response to standard induction therapy, the benefit of full-course standard induction therapy, and the value of high-dose induction therapy.

Selection criteria for future front-line HDT trials. In one recently completed trial (LNH-93[11]) and an additional ongoing randomized trial (UKLG/ANZ/Nordic/EBMT), study patients were selected on the basis of their age-adjusted IPI risk group; eligible patients had either high-intermediate or high-risk disease. The retrospective analyses of the LNH-87 and Italian study group trials also suggested that the benefit of HDT was limited to patients with high-intermediate or high-risk (age-adjusted IPI) disease (level 1-2 evidence).[9,10] For these reasons, the jury concluded that patients who fell into high-intermediate and high-risk categories of the age-adjusted IPI were the most appropriate candidates for future upfront HDT studies (Table 1). The jury also supported the identification of other potentially useful prognostic factors at diagnosis; however, they did not believe that other selection criteria were ready

to be incorporated into large-scale studies at the present time.

Response criteria. To compare recently completed and ongoing randomized phase III trials of HDT in responding patients, the jury also believed that it was essential to adopt uniform definitions of response. Committee members welcomed the ongoing international effort to standardize response criteria for non-Hodgkin's lymphomas (Cheson et al, submitted for publication). In the interim, the jury agreed that complete responses required the disappearance of all evidence of disease on standard radiographs, physical examination, and bone marrow aspirate and biopsy. It was more difficult to accurately delinate complete responders with residual masses from partial responders with persistent viable tumors. The jury strongly encouraged additional investigation into imaging techniques that might distinguish fibrotic residual masses from those containing viable tumor.[17] Nevertheless, committee members acknowledged that such imaging techniques (gallium and/or positron emission tomography scans) are not widely available at the present time. For this reason, current definitions of response continue to be based on routine radiographic studies.

Slow or incomplete responses to standard induction therapy. As noted above, jury members thought that it was difficult to distinguish complete responders with residual masses from partial responders with persistent viable tumor, using standard radiographic criteria. This was a major point of concern when the two randomized studies on the role of HDT in patients with slow or incomplete responses to standard induction therapy were considered (Table 1).[18,19]

In a Dutch cooperative group trial, 69 patients with aggressive NHL in partial response after three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) were randomized to receive HDT or complete an additional five cycles of CHOP.[18] Four-year disease-free and overall survival rates were similar in the two treatment arms (41% and 60% for HDT *v* 72% and 85% for full-course CHOP. P = NS).[18] However, as noted at the consensus conference, the study sample size was too small, the treatment arms were imbalanced with regard to known clinical prognostic factors, and the trial included few high-intermediate or high-risk (IPI) patients.

An Italian multicenter study compared the efficacy of HDT to that of conventional salvage therapy in 49 patients with aggressive NHL in partial response after two thirds of their planned induction therapy.[19] Although progression-free and overall survival rates favored the HDT arm (73% and 73% for HDT *v* 52% and 59% for conventional salvage therapy), these differences were not statistically significant.[19] However, the conference reviewer noted that this study was also too small because ~260 randomized patients would be needed to demonstrate a 33% difference in relative risk between the two treatment arms. The above-mentioned methodologic issues in the two available randomized studies (level 4 evidence [Table 2]) led the jury to conclude that the role of HDT in slow or incomplete responses remains to be defined (Table 1).

HOW TO TRANSPLANT?

After evaluating the settings in which HDT was indicated (when to transplant), the jury next assessed the optimal way to administer HDT (how to transplant, Table 1).

High-Dose Regimens

In the absence of randomized studies comparing specific regimens, the jury concluded that there was not a single superior high-dose protocol (Table 1).[20] The absence of randomized prospective trials made it impossible to determine whether total body irradiation–containing regimens were superior to drug-only programs.[20] Available data on currently used regimens were derived primarily from well-designed single-arm studies, single-institution trials or registries (level 2 evidence).

Hematopoietic Stem Cell Sources

In the jury's opinion, recently completed randomized trials and an earlier case-controlled study supported the use of autologous mobilized peripheral blood stem cells (PBSC) rather than bone marrow in HDT studies (level 1 evidence [Table 1]).[21-25] In a case-controlled analysis, 83 lymphoma patients who received PBSC autografts were compared with 83 additional lymphoma patients who received autologous bone marrow.[22] Patients who were autografted with PBSC had more rapid hematopoietic recovery and fewer episodes of interstitial pneumonitis and fungal infection than those who received bone marrow.[22]

In another randomized trial, 58 patients with Hodgkin's disease or non-Hodgkin's lymphoma who were undergoing HDT received either autologous bone marrow or mobilized PBSC.[23] Time to platelet and neutrophil recovery was significantly shorter in patients receiving PBSC (duration of thrombocytopenia, 16 days for PBSC *v* 23 days for ABMT, P = .02; duration of neutropenia, 11 days for PBSC *v* 14 days for ABMT, P = .005).[23]

Autologous bone marrow and mobilized PBSC support were also compared in a phase III trial of lymphoma and solid-tumor patients undergoing HDT.[24] Hematologic recovery was more rapid in patients who received mobilized PBSC than in those who received bone marrow (duration of thrombocytopenia, 16 days for PBSC *v* 36 days for bone marrow: P = .001).[24]

Similar results were obtained in an additional phase III study in which 89 patients with relapsed or newly diagnosed high-risk intermediate-grade lymphoma were randomized to receive autologous bone marrow or mobilized PBSC after

HDT.[25] In this trial, the median times to neutrophil recovery for patients receiving PBSC or bone marrow were 10 days or 16 days, respectively ($P = .0013$).[25]

Although the above-mentioned trials support the use of mobilized PBSC rather than unprimed bone marrow, a randomized study of mobilized PBSC versus mobilized bone marrow in lymphoma patients undergoing HDT suggests that primed bone marrow is as effective as mobilized PBSC in hematologic reconstitution.[26]

The jury believed there to be insufficient data regarding the potential utility of allogeneic stem cell support in aggressive NHLs (level 4 evidence).[21] Nevertheless, committee members believed that the potential graft versus lymphoma effects associated with allogeneic stem cell transplantation warranted further study. The jury also believed that there were insufficient data regarding the utility of umbilical cord stem cell transplantation in aggressive NHLs (level 4 evidence).[21]

Stem-Cell Mobilization

Committee members agreed that available phase II studies and registry data supported the use of chemotherapy plus cytokines to mobilize hematopoietic stem cells (level 2 evidence [Table 1]).[21] However, they acknowledged that the use of cytokines alone might be warranted in specific clinical settings (level 3 evidence). Similarly, the jury noted that a supplemental ("back-up") marrow might be appropriate in rare individual settings (level 3 evidence).

Purging or Positive Selection

The jury acknowledged single-institution data regarding the potential benefits of purging autologous bone marrow in follicular lymphoma patients undergoing HDT.[27] However, committee members also noted a case-matched registry series in which NHL patients undergoing HDT received purged or unpurged bone marrow and had comparable progression-free survival rates.[28] In an additional single-institution report, NHL patients who received histologically negative bone marrow with minimal tumor cell contamination had shorter relapse-free survival rates after HDT.[29] Committee members believed that at present there were insufficient data (level 4 evidence [Table 1]) to recommend routine purging or positive selection of stem cell products in the aggressive lymphomas. Nevertheless, the group recommended further rigorous analysis of this area.

The jury also addressed a final series of questions regarding the role of HDT in specific clinical settings.

Chemosensitive Marrow Involvement at Relapse

Committee members believed that single-institution data and registry studies supported the use of HDT in patients with chemosensitive bone marrow involvement at relapse. However, the jury noted that most studies evaluated autologous stem cell transplants in this setting[30] (level 2 evidence [Table 1]) and that there was little additional data on comparable allogeneic stem cell transplants (level 4 evidence).

HLA-Matched Sibling Allogeneic Transplants

The jury believed there to be insufficient data on the value of matched sibling allogeneic transplants in patients with recurrent disease after autologous transplantation (level 4 evidence [Table 1]) or in young patients in first relapse (level 4 evidence). Nevertheless, they believed that these areas warranted further study.

FUTURE DIRECTIONS

In the jury's opinion, first or subsequent chemosensitive relapse is an excellent setting in which to evaluate potential improvements in the administration of HDT. Given the demonstrated efficacy of the high-dose regimen used in the PARMA study,[3] such HDT would be an appropriate control arm in future comparative trials of novel regimens, additional forms of radiotherapy, or different sources of hematopoietic stem cells. First or subsequent chemosensitive relapse would also be an appropriate setting to compare autologous versus allogeneic stem cell support, include immunotherapy of minimal residual disease,[31,32] or study novel mobilization regimens containing additional cytokines, such as stem cell factor or FLT 3 ligand.[21]

In newly diagnosed patients, the jury believed that the first priority was to determine the benefit of HDT. Committee members were optimistic that ongoing randomized studies would help clarify the role of HDT in newly diagnosed poor prognosis patients.

The jury also advocated the collection of tumor specimens from newly diagnosed patients for future analyses of biologic prognostic factors that might refine and improve the International Prognostic Index and provide additional insights into novel therapeutic targets.

APPENDIX

The president and members of the jury are as follows: M.A. Shipp, M.D. Abeloff, K.H. Antman, G. Carroll, A. Hagenbeek, M. Loeffler, E. Montserrat, J.A. Radford, G. Salles, and N. Schmitz.

The conference organizers are as follows: M. Symann, J.O. Armitage, T. Philip, and B. Coiffier.

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