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Invited article

High dose therapy and autologous stem cell transplantation for lymphoma: current status

John W. Sweetenham

High dose therapy and autologous stem cell transplantation (ASCT) has been extensively investigated in the treatment of malignant lymphoma, both as salvage treatment, and as a component of first line therapy. Few randomized trials have been conducted, and most evidence is from the retrospective registry-based, or single institution studies. The use of ASCT as salvage therapy for patients with all subtypes of aggressive NHL, or with Hodgkin's disease, who have relapsed after initial chemotherapy, is now a standard of care. In patients with diffuse large B-cell NHL, the survival benefit is restricted to these whose disease is still responsive to 'conventional dose' chemotherapy. The use of ASCT for patients with primary refractory disease is controversial, although retrospective evidence supports its use in patients with Hodgkin's disease, but not those with aggressive NHL. The use of ASCT as a component of first line therapy remains uncertain. For patients with diffuse large B-cell NHL, trials in patients not selected for risk factors have failed to show a survival advantage for ASCT. Trials in patients with 'poor risk' disease as defined by the International Prognostic Index are in progress, and at present, ASCT in this context cannot be recommended except in clinical trials. First remission ASCT for patients with lymphoblastic lymphoma has been compared with conventional dose consolidation therapy. Preliminary results from a single randomized trial show a progression free survival advantage for ASCT in this disease. Although retrospective data have demonstrated encouraging results for this approach in patients with Burkitt's and Burkitt-like NHL, the excellent results of recent dose intensive, non-transplant regimens for these diseases suggest, that first remission ASCT should not be considered a routine for these patients. The potential long term toxicity of ASCT in patients with Hodgkin's disease, and the favorable outcome for this patient group precludes its widespread use as part of the first line therapy, although one randomized trial addressing this issue is in progress.

Zastosowanie chemioterapii w wysokich dawkach z późniejszym przeszczepieniem autologicznych komórek macierzystych szpiku w leczeniu chorych na chłoniaki złośliwe: obecny stan wiedzy

Chemioterapia wysokodawkowana i przeszczepy autologicznych komórek macierzystych szpiku (ASCT) są przedmiotem intensywnych badań klinicznych w leczeniu chłoniaków złośliwych (chłoniaki nieziarnicze i ziarnica złośliwa) zarówno jako program terapii ratunkowej, jak i część terapii pierwszej linii.
Dostępne dane piśmiennicze oparte są albo o wyniki międzyośrodkowych kontrolowanych doświadczeń klinicznych z losowym doborem chorych, albo o dane retrospektywne, albo o wyniki prezentowane przez pojedyncze ośrodki badawcze.
W artykule omówione zostały szczegółowo wskazania do zastosowania ww. procedur wysokospecjalistycznych w leczeniu chłoniaków i ziarnicy złośliwej, ze szczególnym podkreśleniem w jakich przypadkach ASCT może być uznane już dzisiaj za standard leczenia.

Key words: HDT high dose therapy, ASCT — autologous stem cell transplantation, malignant lymphoma
Słowa kluczowe: chemioterapia w wysokich dawkach, przeszczep autologicznych komórek macierzystych szpiku, chłoniaki złośliwe

Introduction

The use of high dose therapy (HDT) and autologous stem cell transplantation (ASCT) for patients with lymphoma has increased rapidly during the last decade. It is now widely accepted as 'standard' salvage therapy in certain patients with relapsed Hodgkin's disease and non-Hodgkin's lymphoma (NHL), where small randomized trials have demonstrated the superiority of HDT over 'conventional' dose salvage therapy. In addition, it is now being assessed as post-remission therapy in some patients with NHL (and to a lesser extent with Hodgkin's dise-

CRC Wessex Medical Oncology Unit
Southampton General Hospital, UK

ase) after an initial remission induction has been achieved with standard dose therapy.

Improvements in supportive care for patients undergoing HDT and ASCT, particularly the use of peripheral blood progenitor cells (PBPCs) in place of bone marrow, have markedly reduced the toxicity of HDT. This has allowed studies of ASCT in first remission to be performed without an excessive risk of treatment-related mortality, and has also increased the upper age limit of patients in whom HDT can be used, thus expanding the potential patient population. These trends, coupled with the well-documented increase in the incidence of NHL, suggest that the potential patient population in whom HDT could be used will increase substantially. It is therefore essential that the impact of HDT and ASCT on survival in these diseases remains a priority for prospective randomized trials.

Although the use of HDT in indolent lymphoma (particularly follicular lymphoma) has been under investigation for several years, no data are currently available from randomized trials in these diseases. More recently, HDT has been used as part of first line and salvage therapy in mantle cell lymphoma, but at present, data are only available from retrospective, or phase II studies. High dose strategies should still be regarded as experimental in these diseases. Most studies of HDT and ASCT in lymphoma have been performed in patients with Hodgkin's disease or aggressive NHL.

Diffuse large B-cell lymphoma (DLBCL)

Salvage therapy

The use of HDT and ASCT as salvage therapy for patients with chemosensitive relapse of DLBCL and other related aggressive subtypes of NHL is now one of the most established uses of this therapy, supported by the results of the PARMA randomized trial [1]. In this study, patients with relapsed, aggressive NHL initially received 2 cycles of DHAP (dexamethasone, high dose cytosine arabinoside, cisplatin). Responding patients were then randomized either to continue with 4 further cycles of DHAP, or to receive high dose therapy using BEAC (carmustine, etoposide, cytosine arabinoside, cyclophosphamide. Involved field radiotherapy was given to sites of initial bulky disease in both arms of the trial. Of the initial 215 patients entered onto the study, 106 were not randomized, either because of failure to respond to the first 2 cycles of DHAP (90) or for various other reasons including patient refusal, or high reported toxicity from DHAP.

At the time of the initial report (median follow up 63 months), the 5 year actuarial event free survival was 46% in the transplant arm, and 12% in the DHAP arm ($p = 0.001$). the corresponding figures for 5 year overall survival were 53% and 32% ($p = 0.038$). The results of the study were updated in 1998, at which time the median follow up was 100 months[2]. The 8 year event free survival rates were 36% in the transplant arm and 11% in the DHAP arm ($p = <0.002$). Corresponding figures for overall survival were 47% and 27% ($p = 0.042$).

These results confirm the superiority of HDT over conventional dose salvage therapy in patients whose disease is still responsive to conventional dose therapy given prior to high dose therapy. HDT and ASCT is standard therapy in this patient group.

The outlook for patients with chemoresistant relapse is very poor, and data from retrospective studies show that long term disease free survival after HDT and ASCT is rare in this group.

First line therapy

Primary refractory disease

Most large retrospective series of HDT and ASCT in aggressive NHL, either registry-based or single center, have included small numbers of patients with primary refractory disease. Very few patients undergoing ASCT in this situation appear to have achieved long term disease free survival. A recent study from Cologne has confirmed this, demonstrating that only a small minority of patients with primary refractory NHL are suitable for HDT, because of age, performance status, rate of disease progression, etc, and that none of the patients receiving HDT and ASCT survived for more that 1 year [3]. A further analysis of outcome for this group is currently being undertaken by the Autologous Blood and Marrow Transplant Registry of North America (ABMTR).

Patients who are 'slow responders' to initial chemotherapy

Previous analyses of patients with aggressive NHL treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or related regimens have shown that patients who have achieved complete remission (CR) after 3 cycles of therapy have a higher probability of long term disease free survival than those who enter remission more slowly, or who fail to achieve complete remission after completion of all therapy.

The use of HDT and ASCT in this situation has been assessed in 2 randomized trials. In a study conducted in the Netherlands, 286 eligible patients with aggressive NHL were initially treated with CHOP chemotherapy, 133 of whom were in partial remission after 3 cycles [4]. Twenty seven of these were ineligible for randomization since they had persistent disease in the bone marrow. Of the remaining 106 patients who were eligible for randomization, only 65 were randomized, either to high HDT (high dose cyclophosphamide and total body irradiation [TBI]), or to continue with 5 further cycles of CHOP. There was no significant difference in 4 year overall (hazard ratio for ASCT *vs* CHOP = 2.2; 95% CI = 0.82 – 5.9; $p = 0.12$) or event free survival (hazard ratio 1.3; 95% CI = 0.66 – 2.61; $p = 0.43$). Martelli et al reported similar findings in 49 patients who were slow responders to MACOP-B or F-MACHOP chemotherapy, and who

were randomized either to receive non-cross resistant, conventional dose therapy with DHAP, or HDT and ASCT [5]. No difference in overall or event free survival was observed according to randomized arm.

HDT/ASCT as a component of first line therapy

Combination chemotherapy using CHOP is currently recognized internationally as standard therapy for patients with advanced aggressive NHL. Numerous single institution phase II studies conducted in the 1980s showed apparently superior response and survival rates for more dose-intensive chemotherapy regimens. However, the large randomized study conducted by the Southwest Oncology Group (SWOG) in the USA showed no difference in response rates, disease free or overall survival when CHOP was compared with m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone), MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin), or ProMACE, CytaBOM (procarbazine, methotrexate, doxorubicin, cyclophosphamide, etoposide, cytosine arabinoside, bleomycin, vincristine, methotrexate) [6]. A British National Lymphoma Investigation (BNLI) randomized trial comparing CHOP with PACEBOM also showed no difference in response rates, disease free or overall survival [7].

In view of the effectiveness of high dose therapy and ASCT for patients with relapsed disease, several randomized studies have been conducted in which patients achieving an objective response to conventional dose induction therapy have been randomized either to continue with conventional dose therapy, or to receive high dose therapy and ASCT. Several such studies were initiated prior to the description of the International Prognostic Index (IPI). Such studies include the GELA LNH-87 trial [8], and the EORTC 20901 trial, both of which assessed the use of 1st remission high dose therapy with no risk stratification. No difference in overall or disease free survival was observed in these studies.

The development of the International Prognostic Index has provided a reproducible clinical model in which clinical features at presentation can be used to stratify patients into prognostic groups [9]. The prognostic model includes 5 adverse factors – advanced age (>60 years), advanced stage, elevated serum lactate dehydrogenase (LDH), > 1 extranodal site of disease and poor performance status. In addition, an age-adjusted prognostic model was developed for patients aged <60 years, including advanced stage, LDH, and performance status only.

Following the description of the IPI, the results of the LNH-87 trial were re-analyzed according to IPI risk groups [10]. Patients in the high/intermediate (H/I) and high (H) risk groups had superior DFS and OS rates when treated with high dose consolidation and ASCT compared with those patients who received conventional dose sequential consolidation therapy (5 year actuarial DFS = 57% for high dose *versus* 36% for conventional dose (p=0.01); 5 year actuarial OS = 65% for high dose versus 52% for conventional dose [p=0.06]). No difference in OS or DFS was observed for patients in the low (L) or low/intermediate (L/I) risk groups. A recent update of these data has confirmed these trends (8 year actuarial DFS = 55% for high dose *versus* 39% for conventional dose (p = 0.02); 8 year actuarial OS = 64% for high dose *versus* 49% for conventional dose [p = 0.04]) [11]. These data must be interpreted cautiously, since they represent a retrospective, subset analysis from a non-stratified prospective clinical trial, but they suggest a possible role for high dose consolidation in patients with poor risk disease.

Several randomized trials of early intensification, using high dose therapy and ASCT have now been reported for poor risk patients, and several others are in progress.

GELA have recently reported results for the LNH--93 trial [12]. This was a randomized comparison of conventional chemotherapy using ACVB (doxorubicin, cyclophosphamide, vinblastine, bleomycin) followed by conventional dose sequential consolidation therapy, compared with and experimental intensified induction regimen CEOP (cyclophosphamide, epirubicin, vincristine, prednisone) plus ECVBP (epirubicin, cyclophosphamide, vindesine, bleomycin, prednisone)) followed by high dose therapy and ASCT. Patients aged <60 years, with 2 or 3 adverse risk factors according to the age-adjusted IPI were eligible. Accrual to the study was closed after an interim analysis. At the time of the most recent report, with a median follow up of 30 months, the 3 year EFS was 54% for the conventional arm *versus* 41% for the high dose arm (p = 0.01), and the 3 year OS was 63% for the conventional dose arm *versus* 47% for the high dose arm (p = 0.003).

The German High Grade Lymphoma Study Group are conducting a study comparing 3 cycles of chemotherapy using CHEOP (cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone) followed by high dose therapy and ASCT, with 5 cycles of CHEOP alone, for patients aged <60, with an elevated LDH. No difference in DFS or OS was reported at the first interim analysis of this trial, or in the most recent update, and analysis using IPI risk groups shows no differences in outcome in any risk groups [13].

The Italian NHL Study Group have recently completed a trial comparing VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone) alone with VACOP-B followed by high dose therapy and ASCT for 'poor risk' patients (defined as bulky stage II, stages III and IV) [14]. When all patients were analyzed, no difference in DFS or OS was observed. Subset analysis showed a significant improvement in DFS for IPI H/I and H risk groups receiving high dose therapy (6 year actuarial DFS = 87% for high dose compared with 48% for conventional dose therapy, p = 0.008). However, no difference in PFS or OS was observed.

Recent studies of 'early' intensification have been notable for the relatively high rate of early progressive disease in patients receiving induction therapy prior to high

dose consolidation. In the GELA LNH-93-3 trial, 29% of patients had progressed before reaching the high dose phase of the trial [15]. Similarly, in the German High Grade Lymphoma Study Group trial, 33% of patients failed to reach the high dose phase, mainly due to disease progression [16]. In The current LY02 trial, the corresponding figure is approximately 30%.

In contrast to most of the studies mentioned above, the GOELAMS group have recently reported initial results of a randomized trial comparing 8 cycles of CHOP chemotherapy with 2 cycles of CEEP (cyclophosphamide, epirubicin, vindesine, prednisone) plus ASCT in patients with non-high risk aggressive NHL according to the age-adjusted IPI [15]. They report a superior 4 year event free and failure free survival in the high dose arm, although there is no overall survival benefit, except in the subgroup with high-intermediate risk disease (3 year OS = 78% vs 43%, p = 0.01).

An alternative approach to dose intensive therapy in NHL has been the development of high dose sequential therapy. This uses non-cross-resistant drugs, given at near maximum tolerated doses, in a sequential fashion, supported by the use of haemopoietic growth factors, and autologous peripheral blood progenitor cells (Figure 1). This

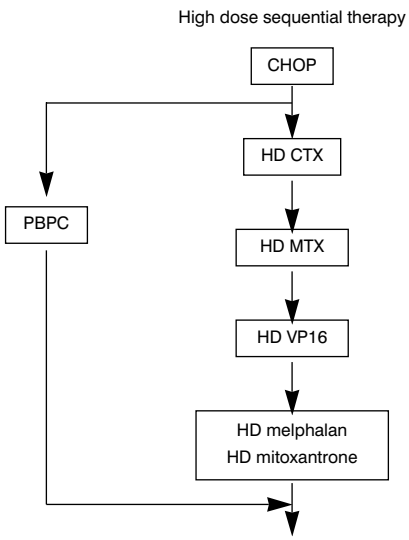

Figure 1. Scheme for high dose sequential therapy

might therefore reduce the potential for early progressive disease which characterizes the protocols described above. The Milan group have recently reported the results of a randomized trial comparing this high dose sequential (HDS) regimen with MACOP-B chemotherapy for patients with poor risk disease (bulky stage I or II, stage III or IV) [18]. 74% of patients in the MACOP-B arm were IPI H or H/I risk, compared with 94% in the HDS arm [16]. A total of 98 patients were randomized. With a median follow up of 55 months at the time of the report, the results were as summarized in Table I.

HDS therapy was well tolerated. Three toxic deaths occurred in the first 30 patients, who received a TBI-based high dose regimen. This was subsequently modified to high dose mitoxantrone and melphalan, and no further toxic deaths have occurred. Overall, much more extramedullary toxicity was observed in patients receiving HDS compared with those receiving MACOP-B.

Table I. Results from randomized comparison of MACOP-B and high dose sequential therapy - adapted from reference 16

	CR	FFP (7yr)	EFS (7yr)	FFR (7yr)	OS (7yr)
HDS	96%	84%	76%	88%	81%
MACOP-B	70%	49%	49%	70%	55%
p	0.001	<0.001	0.004	0.055	0.09

The applicability of this HDS regimen in a multi-center context has been assessed in a pilot study by the Eastern Cooperative Oncology Group (ECOG) in the USA[17]. Twenty patients with 2 or 3 IPI risk factors were treated, with no treatment related deaths. Tolerance of therapy was reported to be good, with a mean of 117 days to complete all 5 phases of therapy, compared with a median of 105 days in the Milan study. The reported CR rate was 80%, although follow-up was too short to analyze survival.

The results of the studies outlined above allow the following preliminary conclusions to be drawn:

- The use of high dose therapy and ASCT in first remission (complete or partial) does not improve DFS or OS for the entire population of patients with advanced aggressive NHL

- Subset analysis of 2 non-stratified trials has shown a DFS and OS advantage for the high dose arm, which is restricted to patients with H/I and H risk disease. No benefit has been observed in these trials for patients with L/I or L risk disease.

- The use of 'early' intensification, using high dose therapy and ASCT prior to the completion of full induction therapy may be inadequate, based on the results of the LNH-93-3 study

- The Milan HDS protocol is the only regimen to date which has produced superior EFS compared with standard dose therapy in poor risk patients in a prospective randomized trial

- The ECOG study has demonstrated that this chemotherapy can be safely delivered in a multi-institutional study.

- Those studies in which sub-set analysis has demonstrated an advantage to high dose therapy have included the high dose regimen at the completion of full induction chemotherapy.

Important studies which may help to clarify the role of ASCT in this setting are still in progress. The LY02 study of the UKLG/Nordic Lymphoma Study Group/EBMT and ANZSLG is comparing 6 cycles of CHOP chemotherapy with 3 cycles of CHOP followed by ASCT in patients with age-adjusted poor risk disease. The current SWOG/ECOG/CALGB study in the United States has a very similar study design.

The UKCCCR has recently joined the SAKK group in Switzerland to conduct the 'MISTRAL' study. The de-

sign of this study is shown in Figure 2. Patients with age--adjusted poor risk aggressive NHL will be randomized between 8 cycles of CHOP chemotherapy, or high dose

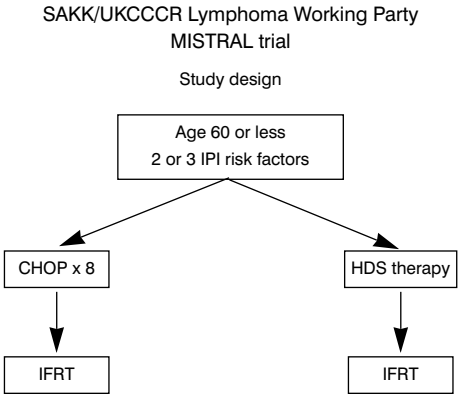

Figure 2. Study design of SAKK/UKCCCR Mistral trial

sequential therapy. This study is powered to detect a 15% improvement in 2 year overall survival from 50% to 65%. It will require 400 randomized patients, and is expected to take 4 years to complete.

Lymphoblastic lymphoma

Salvage therapy

The outlook for adult patients who relapse after induction therapy for lymphoblastic lymphoma (LBL) is poor. Patients treated with conventional dose salvage regimens have a median survival of only 3 to 6 months, with only 5% to 10% of patients achieving long term survival. Reports of the use of HDT and ASCT in this setting have been superior. For example, we have previously reported data from the EBMT registry for patients undergoing ASCT for relapsed LBL [18]. The responsiveness of disease to 2nd line conventional chemotherapy was predictive of outcome. Patients with chemosensitive relapse had long term overall survival of approximately 30%. Even in the group with chemoresistant disease at the time of relapse, 14% achieved long term survival. These results suggest that high dose therapy and ASCT should be considered as standard for patients with LBL who relapse after conventional dose induction, even if the disease is resistant to 2nd line salvage therapy. Although based on registry data only, this is such a rare entity that randomized trials are very unlikely.

HDT/ASCT as a component of first line therapy for LBL

The optimal initial therapy for adult LBL remains uncertain. The use of intensive chemo-/radio-therapy induction regimens, similar to those used for acute lymphoblastic leukemia (ALL) produces response rates of 70% to 80%, with 40% to 60% of patients achieving long term survival. The high complete remission rate, but subsequent high relapse rate has provided the rationale for attempts to consolidate first remission by the use of HDT and ASCT.

Several single center and registry based retrospective studies have reported high long term survival rates for patients receiving HDT and ASCT (or allogeneic BMT) in first remission. In the largest of these, from the EBMT, we reported a 6 year actuarial overall survival rate of 63% in 265 patients treated in this way [18]. Although encouraging, these retrospective data must be interpreted cautiously, and in order to clarify the role of first remission ASCT in this disease, the UKLG and EBMT have conducted a randomized trial, the design of which is shown in Figure 3 [19].

One hundred and nineteen patients were entered into this study, of whom 98 (82%) responded to induction therapy. Of these 65 were randomized, 31 to ASCT and 34 to further conventional therapy. Preliminary results

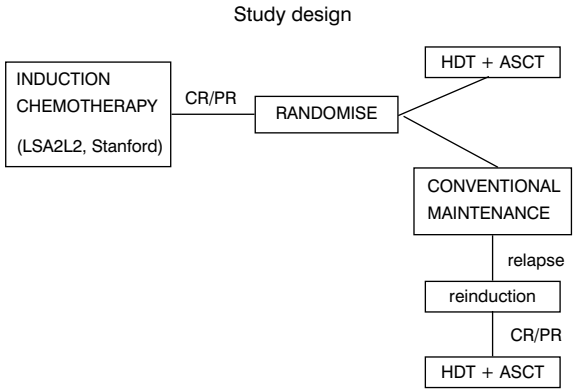

Figure 3. Study design for UKLG/EBMT lymphoblastic lymphoma trial. Choice of induction therapy and of high dose regimen was permissive to maximize accrual.

from the trial are shown in Figure 4. There was a trend for improved relapse free survival in patients receiving high dose consolidation. This did not achieve statistical significance, partly because of the low numbers of patients on the trial. No difference in overall survival was observed. In part, this may be because some of those patients who relapsed after conventional dose consolidation and maintenance therapy received HDT and ASCT if they achieved a 2nd CR to salvage therapy.

Although no survival advantage for 1st remission HDT and ASCT has been shown, the trend for improved relapse free survival suggests that the high dose approach should at least be discussed with patients with this disease. It may reduce the risk of subsequent relapse, and it reduces the overall duration of therapy compared with conventional dose consolidation and maintenance therapy.

Burkitt's and Burkitt-like lymphoma

Salvage therapy

As with LBL, the outlook for patients with these disease who relapse after conventional dose induction therapy is

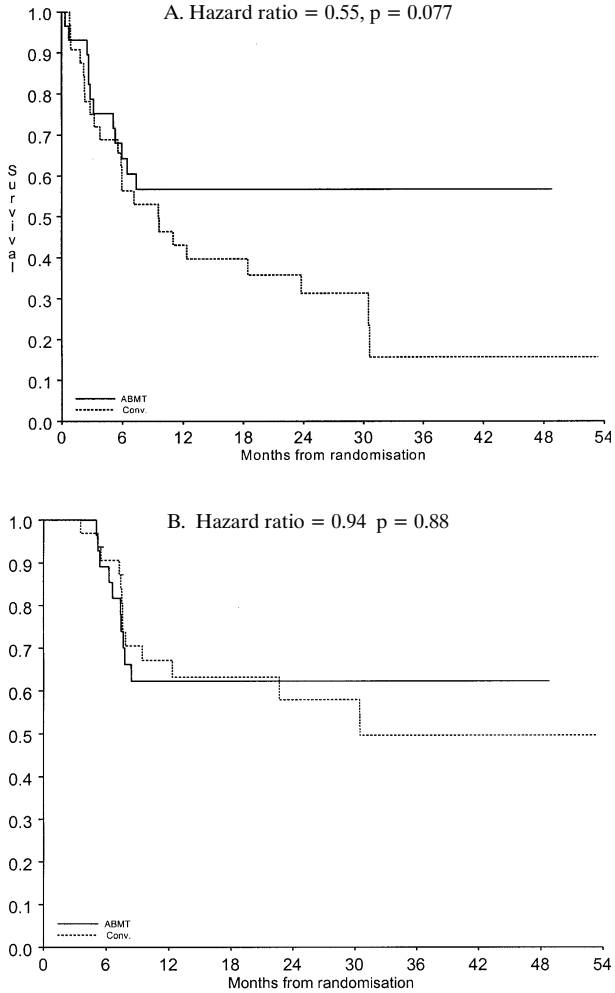

Figure 4. Preliminary results of UKLG/EBMT trial in adult lymphoblastic lymphoma A. Relapse free survival, B. Overall survival

very poor, only around 10% surviving long term, and median survivals of only 3 to 6 months. Results from the EBMT registry show a 3 year actuarial overall survival of 37% for patients treated with HDT and ASCT for chemosensitive relapse, and 7% for those with chemoresistant disease [20]. As with LBL, randomized trials in this setting are very unlikely, and HDT and ASCT should be regarded as standard.

HDT/ASCT as a component of first line therapy

Many dose-intensive combination chemotherapy regimens have been used for patients with Burkitt's and Burkitt-like lymphoma, producing response rates of 60% to 85%, and long term relapse free survival rates of 60% to 80%. Single center and registry-based retrospective series have investigated the role of HDT and ASCT in first remission. In the largest of these studies, from the EBMT registry, we reported 3 year actuarial overall and progression free survival rates of 72% and 73% respectively [20].

Although these results are encouraging, they must be placed in the context of other approaches in these diseases. Magrath et al have recently reported results of the NCI 89-C-41 protocol for adult patients with Burkitt's and Burkitt-like lymphoma [21]. This regimen produced 2 year overall survival rates of over 90%. A multicenter phase I trial of this regimen has recently been completed in Europe. Mature results from this study are awaited, but at present, HDT and ASCT should not be considered as standard therapy in 1st remission, given the excellent results of intensive induction regimens.

Aggressive NHL – summary

Data from randomized trials are still needed to clarify the role of HDT and ASCT in many situations. In those settings where randomized trials will not be undertaken, conclusions about the role of ASCT must be based on retrospective data. Table II summarizes current use of HDT and ASCT in these diseases.

Table II. Summary of current use of high dose therapy and ASCT for aggressive NHL

NHL subtype & status	HDT/ASCT indicated?
chemosensitive relapse	YES
resistant relapse/induction failure	
LBL/Burkitt's/Burkitt-like	YES
DLBCL	NO
First remission	
LBL	YES
Burkitt's/Burkitt-like	NO
DLBCL (all patients)	NO
DLBCL (poor risk)	randomized trials only

Hodgkin's disease

Salvage therapy – following relapse after chemotherapy

The use of 'conventional dose' salvage therapy in patients who relapse after treatment with combination chemotherapy produces high remission rates. In a series from the National Cancer Institute in the USA, in patients relapsing after MOPP (mustine, vincristine, procarbazine, prednisone), re-treatment with MOPP produced second complete remission rates of around 50%, with a median second remission duration of 21 months [22]. The most important prognostic factor for achievement of second remission was the duration of the initial remission. In those patients with an initial remission of less than 12 months, only 29% achieved a second complete remission with MOPP. The second remission rate in those with an initial remission of greater than 12 months was 93%. Despite this high remission rate in the 'favorable' group, only 17% were alive and free of disease at 20 years.

Non-cross resistant regimens have also been widely used as second line therapy for patients with relapsed disease. Encouraging results have been reported in single

center studies using this approach. For example, in studies from Milan, 5 year progression free survival has been reported in 51% of patients treated with further conventional chemotherapy following relapse more than 12 months after treatment with MOPP, ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), or alternating MOPP/ABVD [23]. Various second line regimens were used including MOPP, ABVD or CEP (lomustine, etoposide, prednimustine).

These results have not been reproduced in multi-center studies. In a randomized study conducted by the Cancer and Leukemia Group B (CALGB), patients receiving ABVD as first line therapy were treated with MOPP at relapse, with a 5 year failure free survival rate of only 31% [24]. The outcome for patients who received MOPP as initial therapy, and ABVD at relapse was worse, with only 15% failure free at 5 years.

Results of the use of HDT and ASCT in this setting have been superior. Chopra et al have reported a 5 year freedom from progression rate of 47% in a series of 52 patients receiving HDT and ASCT at first relapse after combination chemotherapy [25]. Comparable results were reported from Vancouver in 58 patients receiving HDT and ASCT in first relapse, in whom the 5 year freedom from progression was 61% [26]. In a study from Stanford University, the outcome for 60 patients with relapsed or refractory disease treated with HDT and ASCT was compared with a matched group of historical controls who received conventional dose salvage therapy [27]. Four year event free survival (EFS) and freedom from progression (FFP) were higher in the group treated with HDT and ASCT although no overall survival difference was observed. For the group of patients who relapsed after an initial remission of less than 1 year, an overall survival advantage was observed for patients receiving high dose therapy.

In a registry-based study from the European group for Blood and Marrow Transplantation (EBMT) we reported a 45% event free survival at 5 years in 139 patients with Hodgkin's disease treated with HDT and ASCT in first relapse after chemotherapy [28].

The results of two randomized trials comparing high dose with conventional dose salvage therapy have now been reported. In a small randomized trial conducted by the British National lymphoma Investigation (BNLI), 40 patients with Hodgkin's disease in first or subsequent relapse were randomized to receive high dose therapy with BEAM (carmustine, etoposide, cytosine arabinoside, melphalan) and autologous bone marrow transplantation (ABMT) or conventional dose therapy, using the same drugs at lower dose ('mini-BEAM') [29]. There was a significant difference in EFS for patients receiving BEAM compared with mini-BEAM (3 year EFS = 53% for BEAM versus 10% for mini-BEAM, $p = 0.025$), although there was no overall survival difference. The overall survival in this study is, however, difficult to interpret, since some patients who relapsed after mini-BEAM 'crossed over' to receive BEAM and ASCT and were subsequently progression free.

The German Hodgkin's Disease Study Group and EBMT have recently completed a randomized study with a similar design [30]. One hundred and sixty one patients with relapsed Hodgkin's disease were entered. All were initially treated with 2 cycles of Dexa-BEAM (dexamethasone, BEAM (carmustine, etoposide, cytosine arabinoside, melphalan). Responding patients were then treated according to randomized arm, either with 2 further courses of Dexa-BEAM, or BEAM and ASCT. One hundred and thirty nine patients were evaluable. With a median follow up of 34 months, there was a significant improvement in time to treatment failure (TTF) for patients receiving BEAM and ASCT compared with those receiving further DexaBEAM. However, there was no difference in overall survival. As with the BNLI study, this is partly due to the ability of HDT and ASCT to salvage patients who relapsed after receiving conventional dose therapy.

Salvage therapy – after failure of induction chemotherapy

Patients who do not enter remission after first line combination chemotherapy have a poor outlook. In a study from Milan, 41% of patients who failed to respond to alternating MOPP/ABVD and were treated with the CEP regimen, achieved a complete response, but only 12% were alive at 5 years, and all of these had active disease [31]. Similar results were reported from the National Cancer Institute in the USA [22,] with a 16 month median overall survival, and from Stanford University, where the 4 year overall survival for patients with primary refractory Hodgkin's disease was only 38%, with a corresponding 4 year PFS of 19% [27].

Several retrospective studies have reported encouraging results in patients treated with HDT and ASCT after failure to enter remission. In a series from London, 46 patients with primary refractory Hodgkin's disease were treated with BEAM and ABMT [25]. The 5 year PFS for this group was 33%. Comparable results have been observed in Milan using high dose sequential therapy with ASCT [32]. The group from Stanford reported a 4 year PFS of 52% and OS of 44% in patients with primary refractory disease receiving HDT and ASCT. These results were significantly better than those for a matched population of historical controls who received conventional dose second line therapy [27, 33].

The Autologous Blood and Marrow Transplant Registry of North America (ABMTR) have recently reported a series of 122 patients with Hodgkin's disease who underwent HDT and ASCT having failed to achieve remission after induction chemotherapy [34]. Definition of induction failure in this series was restricted to patients who had obvious disease progression after induction therapy, or who had biopsy-proven persistent disease in residual radiographic abnormalities. The 3 year actuarial PFS and OS in this series were 38% and 50% respectively. The EBMT have reported comparable results in 175 patients with Hodgkin's disease failing to enter remission

after one or two induction chemotherapy regimens [35]. This series included patients with disease progression, and those with either stable, or minimally responsive disease following initial chemotherapy. The 5 year actuarial PFS and OS were 36% and 32% respectively.

Although the results of HDT and ASCT appear superior, all of these results must be interpreted cautiously. In addition to the potential selection bias inherent in retrospective analyses, the definition of induction failure is inconsistent in these studies. Assessment of response in Hodgkin's disease is problematic, particularly in patients with bulky mediastinal disease at presentation, where residual masses are common after chemotherapy [36, 37]. These masses may contain active disease, but may represent fibrotic masses with no active disease. The group of patients who have stable, or only minimally responsive disease after chemotherapy may therefore be distinct from those who have obvious disease progression.

Only two of the published series have attempted to address this issue. In the ABMTR series, only patients with definite disease progression, or those with tissue confirmation of disease in residual masses were included. In the EBMT series, there was no difference in outcome for patients who had obvious disease progression after first line therapy, compared with those who had stable, or minimally responsive disease.

HDT/ASCT as a component of first line therapy in 'poor risk' Hodgkin's disease

In view of the apparent activity of HDT and ASCT for relapsed and refractory Hodgkin's disease, it has also been used as a component of first line therapy in patients with 'poor risk' disease. In most reports, HDT has been given to consolidate complete remission in patients thought to be at high risk of subsequent relapse. These retrospective studies have observed long-term disease-free survival rates of 70% to 90% [38-41].

However, interpretation of these data is difficult because of their retrospective nature and the variable definition of poor risk disease. A prospective, randomized trial comparing conventional dose chemotherapy using ABVD with HDT and ASCT is in progress, but the definition of 'poor risk' in the eligibility for this trial is controversial [42].

The International Prognostic Factors Project on Advanced Hodgkin's Disease have recently described reproducible clinical prognostic factors at presentation for patients with advanced Hodgkin's disease [43], but these were not available when the present randomized study was initiated.

However, irrespective of the results of this trial, the role of HDT and ASCT as a component of first line therapy is doubtful. The projected long-term disease free survival for the poorest risk group in the International Prognostic Factors Project was approximately 40%. Emerging reports of the long-term toxicity of high dose therapy have identified major effects on reproductive function in both sexes, as well as a risk of secondary malignancy.

In view of the effectiveness of HDT and ASCT as salvage therapy, poor risk patients should probably receive conventional dose, anthracycline-based induction therapy, reserving HDT and ASCT for patients with relapsed or refractory disease. This approach will mean that 40% of patients with poor risk disease will not be exposed to the potential short- and long-term toxicity of HDT, and the overall survival for the entire cohort of patients is unlikely to be compromised.

Hodgkin's disease – summary

Current use of HDT and ASCT for patients with Hodgkin's disease is summarized in Table III. Although there have been few randomized trials, the use of HDT/ASCT as salvage therapy is now well-established for patients in 2nd or subsequent relapse after chemotherapy, and for those in first relapse with an initial remission duration of >1 year. In patients with a shorter initial remission, the poor long term results of conventional dose salvage justify a high dose approach also. At present, there is no role for HDT and ASCT in the first line treatment of Hodgkin's disease.

Table III. Summary of current use of high dose therapy and ASCT for patients with Hodgkin`s disease

status	HDT/ASCT indicated?
2nd or subsequent relapse	YES
First relapse after chemotherapy - initial remission < 1 year	YES
First relapse after chemotherapy - initial remission >1 year	YES
Induction failure	YES
1st remission in 'poor risk' patients	NO (randomized trials only)

John W. Sweetenham M.D. Ph.D.
University of Colorado Health Sciences Center
Division of Medical Oncology-B171
4200 East Ninth Avenue
Denver
Colorado 80262
USA

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