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Research Article

# High dose chemotherapy with autologous stem cell transplantation in diffuse large B-cell lymphoma

## Hochdosistherapie mit autologer Stammzelltransplantation bei Patienten mit diffus großzelligem Non-Hodgkin-Lymphom

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## Abstract

**Background:** High-dose chemotherapy (HDT) with autologous stem cell transplantation (ASCT) plays an important role in the treatment of aggressive non-Hodgkin's lymphoma (NHL). We report on a retrospective analysis of all patients with diffuse large B-cell lymphoma who were consecutively treated with HDT followed by ASCT at the University Hospital of Bonn, Germany, between 1996 and 2004.
**Methods:** A total of 25 patients were transplanted for biopsy-proven diffuse large B-cell lymphoma (DLBCL). Eight patients received up-front HDT as first-line therapy, four patients received HDT due to incomplete response to conventional induction chemotherapy, and six patients were treated for primary refractory disease. Seven patients had recurrent lymphoma.
**Results:** A complete remission (CR) was achieved in 14 of 25 patients (56%). Estimated 3-year survival for patients treated with upfront HDT, chemosensitive patients with incomplete response to first line therapy, and patients with chemosensitive relapsed disease was 87.5%, 50.0% and 60.0%, respectively. In contrast, no patient with primary refractory disease or relapsed disease lacking chemosensitivity lived longer than 8 months. Chemosensitivity was the only significant prognostic factor for overall survival (OS) in multivariate analysis.
**Conclusions:** Our results confirm that HDT and ASCT is a highly effective therapy in patients with DLBCL leading to long-term survival in a substantial proportion of patients. Patients treated upfront for high-risk disease, incomplete response to conventional first-line therapy, or for chemosensitive relapse have a good prognosis. In contrast, patients with primary chemorefractory disease and patients with relapsed disease lacking chemosensitivity do not benefit from HDT with ASCT.

**Keywords:** diffuse large B-cell lymphoma, high-dose chemotherapy, autologous stem cell transplantation

## Zusammenfassung

**Hintergrund:** Die Hochdosistherapie (HDT) mit autologer Stammzelltransplantation (SZT) spielt in der Behandlung aggressiver Non-Hodgkin-Lymphome (NHL) eine große Rolle. Wir präsentieren die Ergebnisse einer retrospektiven Analyse sämtlicher Patienten mit diffus großzelligem Non-Hodgkin-Lymphom (DLBCL), die im Zeitraum zwischen 1996 und 2004 an der Universitätsklinik Bonn mittels HDT und nachfolgender autologer SZT behandelt worden sind.
**Methoden:** Insgesamt wurden 25 Patienten mit bioptisch gesichertem DLBCL transplantiert. Bei acht Patienten erfolgte die HDT als geplanter Bestandteil der Erstlinientherapie („up-front"), vier Patienten wurden wegen inkompletten Ansprechens und sechs wegen primärer Refraktärität auf die konventionelle Chemotherapie transplantiert. Sieben Patienten erhielten die HDT wegen eines Rezidivs des DLBCL.

**Ergebnisse:** Eine komplette Remission wurde bei 14 der 25 Patienten (56%) erreicht. Die geschätzten 3-Jahres-Überlebensraten von Patienten, die die HDT als Teil der Erstlinientherapie erhielten, lag bei 87,5%; für chemosensitive Patienten mit inkomplettem Ansprechen auf die Erstlinientherapie und Patienten mit chemosensitiver rezidivierter Erkrankung lagen die entsprechenden Werte bei 50% bzw. 60%. Demgegenüber lebte in der Gruppe der primär refraktären bzw. rezidivierten Patienten ohne erhaltene Chemosensitivität kein Patient länger als 8 Monate. In der multivariaten Analyse prognostisch relevanter Faktoren für das Gesamtüberleben erwies sich Chemosensitivität als einzig signifikanter Parameter.

**Schlussfolgerung:** Unsere Ergebnisse zeigen, dass die HDT mit nachfolgender SZT in der Behandlung von Patienten mit DLBCL eine hocheffektive Therapie darstellt, die bei einem Großteil der Patienten ein Langzeitüberleben ermöglicht. Patienten, die die HDT in Hochrisikosituationen als Teil der Erstlinientherapie erhalten oder wegen inkompletten Ansprechens auf konventionelle Chemotherapie bzw. im chemosensiblen Rezidiv transplantiert werden, haben eine gute Prognose. Im Gegensatz dazu profitieren Patienten mit primär refraktärer Erkrankung und Patienten mit chemoresistentem Rezidiv nicht von einer HDT.

**Schlüsselwörter:** diffus großzelliges Non-Hodgkin-Lymphom, Hochdosistherapie, autologe Stammzelltransplantation

## Introduction

High-dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT) is an established treatment approach for certain subgroups of patients with aggressive non-Hodgkin's lymphoma (NHL). For patients with relapsed aggressive NHL sensitive to second-line salvage chemotherapy, prolonged event-free survival has been demonstrated in the well-known Parma trial [1]. As a result of this single randomised trial, HDT with ASCT is widely accepted as standard treatment in this patient population.

Although some phase I/II trials have reported favourable results for HDT with ASCT as first-line therapy for patients considered to be at high risk for relapse, results of larger, prospective randomised trials have been contradictory [2], [3], [4], [5], [6], [7], [8], [9], [10]. In some trials applying the international prognostic index (IPI) retrospectively, patients with high-intermediate and high-risk profiles had significantly better results with HDT followed by ASCT than those treated with conventional chemotherapy [11], [12], [13], [14], [15]. As a consequence, more recently designed trials prospectively evaluated the effect of HDT with ASCT in consideration of the IPI. In a meta-analysis of eleven randomised trials comparing HDT with ASCT to conventional chemotherapy, HDT/ASCT was superior in terms of OS in high and high-intermediate risk patients when this strategy is used after maximum tumour reduction has been achieved [16]. However, combined analysis of the different available trials is hampered - if not impossible - due to considerable heterogeneity between the trials in terms of patient selection as well as study design. As superiority of HDT followed by ASCT in first line therapy of aggressive NHL has still not been conclusively demonstrated, this treatment approach has still to be considered experimental and is a source of ongoing controversial discussions.

The answer to the question whether HDT is appropriate in patients with *chemorefractory* first or subsequent relapse or primary refractory disease is controversial and made difficult due to the lack of uniform criteria to define chemorefractoriness disease in different clinical trials. Jury members of an "International Consensus Conference on High-Dose Therapy with Haematopoietic Stem Cell Transplantation in Aggressive NHL" held in April 1998 agreed that HDT was not indicated for chemorefractory first or subsequent relapse [17]. On the other hand, a small subset of patients with primary refractory disease might benefit from HDT [18], [19], [20], [21]. Therefore, some patients with induction failure can have long-term disease-free survival with HDT and ASCT.

In an attempt to contribute to the available information regarding the role of HDT with ASCT in NHL treatment, we here report on a detailed retrospective analysis of all consecutively treated patients with diffuse large B-cell lymphoma who were treated with HDT and ASCT at the University Hospital of Bonn, Germany, between 1996 and 2004. Subgroup analysis and univariate as well as multivariate analysis with regard to factors predicting outcome are presented. Results are discussed against the background of the existing body of evidence.

# Methods

## Patients

Between 1996 and 2004, a total of 52 patients underwent high-dose chemotherapy (HDT) with autologous stem cell transplantation (ASCT) for malignant lymphoma at the University hospital of Bonn, Germany. To ensure homogeneity of the analysed population and to exclude selection bias due to different histologies, this retrospective analysis includes 25 patients with biopsy-proven diffuse large B-cell lymphoma (DLBCL) only. All patients had adequate organ function as defined by a creatinine clearance more than 60 ml/min; adequate cardiac function (ejection fraction ≥50%), serum transaminases less than three times the normal value; bilirubin less than 3 mg/dl; adequate haematopoietic sufficiency (leukocyte count ≥3.0 G/l and platelet count ≥80 G/l), no active uncontrolled infection or human immunodeficiency virus (HIV)-positive serology, and an performance status of ≥2 according to the Eastern Cooperative Oncology Group classification scale.

## Determination of disease status pre-transplant

For operative purposes, pre-transplant disease status as well as indication for HDT followed by ASCT was categorised as follows: All patients who received HDT with ASCT as upfront induction therapy in form of a "high-dose sequential therapy" and patients undergoing consolidative HDT with ASCT after achieving a complete remission (CR) with conventional induction therapy were grouped together. Patients failing to achieve a CR to anthracycline-based 1$^{st}$-line chemotherapy were separated in two groups: Patients with only incomplete response to conventional induction chemotherapy achieving at least a partial remission (PR) after subsequent pre-transplant salvage chemotherapy were considered to have *primary refractory, chemosensitive disease*. In contrast, patients with either progressive disease (PD) during first-line chemotherapy or only stable disease (SD) or PD after completion of induction therapy or failing to respond to subsequent pre-transplant salvage chemotherapy were defined to have *primary refractory, chemoresistant disease*. Similarly, patients with relapsed disease were separated according to their response to salvage chemotherapy: *Chemorefractory relapse* was defined as SD or PD after two courses of an aggressive salvage regimen, whereas achievement of at least a PR after two cycles of aggressive salvage therapy was regarded as *chemosensitive relapsed disease*.

## Staging, follow-up and response criteria

Initial staging procedures at first diagnosis or time of relapse followed standard guidelines. Physical examination, complete blood counts, serum chemistry, bone marrow aspiration and biopsy, and radiological studies were performed in all cases. Restaging examinations were performed after every two courses of conventional therapy, immediately pre-transplant and four weeks after HDT/ASCT. During the first two years of follow-up, physical examination, laboratory examinations and CT scans or ultrasonography of involved regions were repeated every three months. During the third and fourth year post-transplant, follow-up visits were scheduled every six months and annually thereafter.

Response was assessed according to standardised criteria following the recommendations of a National Cancer Institute (NCI)-sponsored international working group [22]. Patients were classified according to the international prognostic index (IPI) at diagnosis or at time of relapse according to the original publication [23].

## Stem cell harvest and cryopreservation

The source of haematopoietic progenitors was peripheral blood in all patients. Harvested peripheral stem cells were processed on a COBE®SpectraTM separator and the mononuclear cells were cryopreserved in 10% dimethylsulfoxide (DMSO) with 20% autologous plasma and kept in liquid nitrogen. Quality testing included viability testing and assessment of the colony forming unit (CFU) capacity. Maximum period of stem cell storage has been limited by internal standards to 5 years.

## Transplantation procedure

Patients received one of the following conditioning regimens: *Mega-CHOEP* (cyclophosphamide 1500 mg/m$^2$, adriamycin 70 mg/m$^2$, vincristine 2 mg, etoposide 800 mg/m$^2$, and prednisone 500 mg (1$^{st}$ course), cyclophosphamide 2250 mg/m$^2$, adriamycin 70 mg/m$^2$, vincristine 2 mg, etoposide 960 mg/m$^2$, and prednisone 500 mg (2$^{nd}$ and 3$^{rd}$ course), and cyclophosphamide 6000 mg/m$^2$, adriamycin 70 mg/m$^2$, vincristine 2 mg, etoposide 1480 mg/m$^2$, and prednisone 500 mg (4$^{th}$ course): 11 patients; *BEAM* (BCNU 300 mg/m$^2$, etoposide 1200 mg/m$^2$, cytosine arabinoside 1600 mg/m$^2$, and melphalan 140 mg/m$^2$): 6 patients; *CEI* (carboplatin 1500 mg/m$^2$, etoposide 2400 mg/m$^2$ and ifosfamide 10 g/m$^2$): 5 patients; *CEIAP* (carboplatin 1000 mg/m$^2$, etoposide 1200 mg/m$^2$, ifosfamide 7500 mg/m$^2$, adriamycin 50 mg/m$^2$, dexamethasone 60 mg): 2 patients; and the *IC* regimen (thiotepa 750 mg/m$^2$, busulfan 10 mg/kg, and cyclophosphamide 120 mg/kg) in one patient. Stem cells were infused on day 0.

## Supportive care during neutropenic phase

All patients were treated in single- or two-bed rooms. Patients received a diet low in bacterial and fungal content. Antimicrobical, antifungal, and antiviral prophylaxis consisted of oral co-trimoxazole, itraconazole, amphotericin suspension, and acyclovir, respectively. Parenteral antibi-

otics were started if fever ≥38°C occurred during neutropenia and maintained until defervescence for at least three consecutive days. In the absence of significant bleeding, platelet transfusions were administered as required to maintain a platelet count of greater than 10 x $10^9$/L. Transfusions of packed red blood cells were given on an individual basis. In most patients, a target haemoglobin concentration of >8 g/dl was aimed at. A decision on the administration of granulocyte colony-stimulating factor (G-CSF; filgrastim) was made on an individual basis. Parenteral nutrition and analgetic treatment for mucositis was used as clinically indicated.

## Toxicity

Toxicity was assessed according to the common toxicity criteria of the National Cancer Institute.

## Statistical analysis

Demographics and disease characteristics were summarised using descriptive statistics. Survival analysis was performed using the Kaplan-Meier method and by applying the log rank test. Overall survival was measured from entry onto trial until death from any cause. Progression-free survival was measured from the time of entry onto study until disease progression or death from NHL. Survival was analysed using the method of Kaplan and Meier and was compared between groups using the log-rank test.

To determine prognostic factors for overall survival, patient characteristics were subjected to univariate analysis for each of the following variables: age (≤50 vs. >50 years), sex, disease stage (I or II versus III or IV according to Ann Arbor), performance status (ECOG 0 vs. ECOG 1 or 2), baseline lactate dehydrogenase (LDH) levels, number of involved extranodal sites (≤1 vs. >1), number of prior chemotherapy regimens (≤1 vs. >1), IPI (low or low-intermediate vs. high-intermediate or high), presence of bulky disease, presence of bone marrow involvement, number of HDT courses applicated, chemosensitivity prior to transplantation, and pre-transplantation disease status (CR vs. not in CR).

All tests were two-sided and the level of significance was set to 0.05. Multivariate analysis with those variables of at least borderline significance in univariate analysis (p-value <0.08) was performed according to the Cox proportional hazard regression model. Statistical calculations were performed using SPSS software (version 11.0.1).

# Results

Efficacy and toxicity as well as long-term follow-up data were available for all but one patient, who was lost to follow-up due to non-European residency.

## Patient characteristics

Baseline clinical features of all patients are shown in Table 1. Eight patients received up-front HDT/ASCT or consolidative HDT followed by ASCT after achievement of a CR to conventional first-line therapy, ten patients received HDT/ASCT for induction failure. Four of these patients had an incomplete response to conventional induction chemotherapy still responsive to salvage chemotherapy while six patients were categorised to have primary refractory, chemoresistant disease. Seven patients had recurrent lymphoma. Chemosensitive relapse was present in five patients whereas two patients were treated for chemoresistant disease.

Thirteen of 25 (52%) patients had high-intermediate or high risk disease according to the IPI. Bulky disease was present in 40% of patients and 3 of 25 (12%) had bone marrow involvement. The baseline LDH level at time of diagnosis or time of relapse was elevated in 23 of 25 (92%) patients. Two patients were in CR prior to transplantation.

## Efficacy

Response rates and survival data are summarised in Table 2. After HDT followed by ASCT, a CR rate of 56% was achieved. Patients treated with up-front HDT/ASCT had the best outcome with 87.5% patients achieving a CR or CRu. Six of eight patients in this group had at least an IPI score ≥3 and all had elevated LDH levels at diagnosis. CR and overall remission rates (ORR) did not differ significantly between patients with chemosensitive relapse or patients with only incomplete response to 1$^{st}$-line therapy but chemosensitive disease. In contrast, none of the primary refractory, chemoresistant patients, and only one patient in the relapsed chemorefractory patient group, achieved a CR.

Survival curves for patients with different pre-transplantation disease status are shown in Figure 1. According to the log-rank test, a highly significant difference with regard to overall survival was observed. Whereas median survival in patients treated with upfront HDT/ASCT or patients with chemosensitive disease has not been reached, none of the ten patients with chemorefractory disease pre-transplant achieved long-term disease free survival after transplantation. In contrast, neither disease stage (Ann Arbor stage I or II versus III or IV) nor IPI score (low or low-intermediate versus high-intermediate or high) had a significant impact on overall survival.

At a median follow-up of 42 months (10-110), 12 patients (48%) are alive. Causes of death were PD in ten patients (40%) and three patients 12% died of infectious complications, all of whom were directly related to the immunosuppression during the transplantation-procedure. No secondary malignancies or myelodysplastic syndrome (MDS) have been recorded to date.

Table 1: Patient characteristics

| Patient characteristics | No. of patients | % |
|---|---|---|
| **Demographic data** | | |
| No. of patients | 25 | |
| Age (median, range in years) | 43 (18-69) | |
| 50 years and younger | 15 | 60 |
| Sex | | |
| male | 13 | 52 |
| **ECOG performance status** | | |
| 0 | 13 | 52 |
| 1 | 11 | 44 |
| 2 | 1 | 4 |
| **Bone marrow involvement** | 3 | 12 |
| **elevated baseline LDH level** | 23 | 92 |
| **Extranodal involvement at >1 site** | 15 | 60 |
| **baseline haemoglobin level (median, range)** | 11.3 | 9.5-14.9 |
| **"Bulky" disease (>7.5 cm)** | 10 | 40 |
| **Disease status** | | |
| Upfront HDT or consolidation | 8 | 32 |
| Primary refractory, *chemosensitive* disease | 4 | 16 |
| Primary refractory, *chemoresistant* disease | 6 | 24 |
| Relapsed disease, *chemosensitive* | 5 | 20 |
| Relapsed disease, *chemoresistant* | 2 | 8 |
| **Number of previous chemotherapy regimens** | | |
| max 1 or upfront HDT | 13 | 52 |
| 2 | 9 | 36 |
| 3 | 3 | 12 |
| **Ann Arbor Stage** | | |
| I (A and B) | 2 | 8 |
| II (A and B) | 9 | 36 |
| III (A and B) | 3 | 12 |
| IV (A and B) | 11 | 44 |
| **Disease stage pre-transplant** | | |
| CR (complete remission) | 2 | 8 |
| PR (partial remission) | 15 | 60 |
| SD (stable disease) | 4 | 16 |
| PD (progressive disease) | 4 | 16 |
| **IPI or 2$^{nd}$-line IPI score at protocol entry** | | |
| Low (0–1 risk factors) | 6 | 24 |
| Low-intermediate (2 risk factors) | 6 | 24 |
| High-intermediate (3 risk factors) | 12 | 48 |
| High (4 or 5 risk factors) | 1 | 4 |

Table 2: Efficacy: Remission rates after HDT followed by ASCT and 3-year OS

| disease status*: | all patients n=25 | "up-front"* n=8 | 1st-line sensitive* n=4 | 1st-line resistant' n=6 | 2nd-line sensitive* n=5 | 2nd-line resistant* n=2 | p-value*** |
|---|---|---|---|---|---|---|---|
| **Response data**** | | | | | | | |
| **CR/ CRu (%)** | 14 (56.0) | 7 (87.5) | 2 (50.0) | 1 (16.7) | 4 (80.0) | 0 (0.0) | 0.029* |
| **PR (%)** | 7 (28.0) | 1 (12.5) | 2 (50.0) | 3 (50.0) | 0 (0.0) | 1 (50.0) | |
| **PD (%)** | 1 (4.0) | 0 (0.0) | 0 (0.0) | 1 (16.7) | 0 (0.0) | 0 (0.0) | |
| **n.e. (%)** | 3 (12.0) | 0 (0.0) | 0 (0.0) | 1 (16.7) | 1 (20.0) | 1 (50.0) | |
| **Survival data** | | | | | | | |
| **3-Year OS (n=25)** | 48.0% | 87.5% | 50% | 0% | 60% | 0% | |
| **median OS (months)** | 17.1 | n.r. | 13.4 | 3.58 | n.r. | 0.72 | 0.0001 |

* disease status:
"up-front" = up-front sequential HDT or consolidation HDT after achievement of a CR with conventional first-line therapy
1st-line sensitive = primary refractory, *chemosensitive* disease
1st-line resistant = primary refractory, *chemoresistant* disease
2nd-line sensitive = relapsed patients, *chemosensitive* disease
2nd-line resistant = relapsed patients, *chemoresistant* disease
(detailed information in the results section)

Response criteria:
CR/CRu = complete remission or unconfirmed complete remission
PR = partial remission
PD = progressive disease
n.e. = not eligible
*** p-value: Achievement of CR versus non-achievement of CR after HDT/ASCT

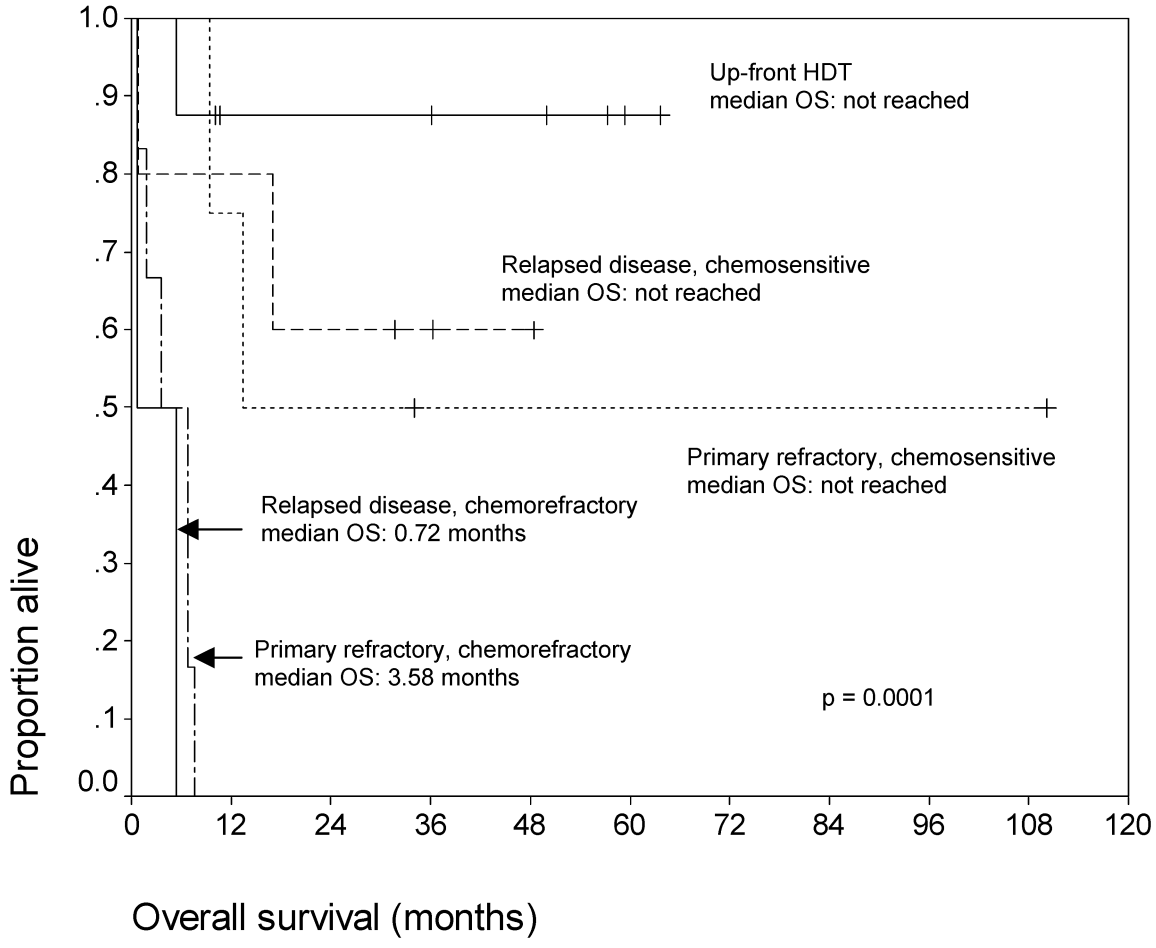


Figure 1: Kaplan-Meier curve of overall survival according to disease status pre-transplant

Table 3: Significant prognostic factors for OS in univariate and multivariate analysis

| Variable | univariate p | multivariate p |
|---|---|---|
| *Age* | | |
| ≤50 | 0.604 | |
| >50 | | |
| *Sex* | | |
| male | 0.124 | - |
| female | | |
| *Stage* | | |
| I or II | 0.814 | - |
| III or IV | | |
| *Performance status* | | |
| ECOG 0 | *0.038* | 0.082 |
| ECOG 1 or 2 | | |
| *baseline LDH level* | 0.066 | 0.766 |
| *Extranodal disease* | | |
| ≤1 site | 0.833 | - |
| >1 site | | |
| *IPI* | | |
| I or II | 0.519 | - |
| III or IV | | |
| *"Bulky" disease* | | |
| yes | 0.485 | - |
| no | | |
| *No. of prior regimens* | | |
| ≤1 | 0.135 | - |
| >1 | | |
| *Bone marrow involvement* | | |
| no | 0.339 | - |
| yes | | |
| *No. of HDT regimens* | | |
| 1 | 0.287 | - |
| 2 or 3 | | |
| *Chemosensitivity* | | |
| no | *<0.0001* | *<0.001* |
| yes | | |
| *Disease status pre-transplant* | | |
| CR | 0.405 | - |
| no CR | | |

## Analysis of pre-transplant prognostic factors for OS

Performance status, presence of chemosensitivity and LDH baseline levels were of prognostic importance with regard to OS in univariate analysis and were entered into multivariate Cox regression analysis. Only chemosensitivity to salvage chemotherapy pre-transplant remained predictive of OS (p=0.001). Table 3 lists the p-values for OS.

## Toxicity

HDT with ASCT was associated with substantial haematologic as well as non-haematologic toxicities. All 25 patients achieved complete haematologic engraftment with absolute neutrophil counts >0.5 × G/l after a median of 10 days (range, 4 to 30 days) and a self-sustaining platelet count >50 × G/l after a median of 9 days (range, 3 to 25 days). 19 patients (76%) received G-CSF for a median of 10 (2–15) days. Twenty patients (80%) required packed red cell transfusions (median 4 units). Platelet transfusions were given to 23 (92%) of patients (median 2 units). There were three deaths, all of whom were infection-related. Detailed information on severe non-haematologic toxicities is provided in Table 4. No

**Table 4: Highest degree of treatment-related non-haematological toxicity observed in n=25 patients receiving high-dose chemotherapy followed by autologous transplantation for diffuse large B-cell lymphoma**

| Non-haematological toxicity | Grade 3 (%) | Grade 4 (%) |
|---|---|---|
| Nausea/emesis | 1 (4) | 0 (0) |
| Diarrhea | 2 (8) | 1 (4) |
| Neutropenic fever | 11 (44) | 2 (12) |
| Mucositis | 2 (8) | 3 (12) |
| Nephrotoxicity | 2 (8) | 2 (8) |
| Cardiac arrhythmias | 1 (4) | 0 (0) |

cases of secondary acute myeloid leukemia (AML) or MDS were documented.

## Discussion

In this paper, we present outcome data of all patients with diffuse large B-cell lymphoma (DLBCL) who have been treated with high-dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT) between 1995 and 2004 at the University Hospital of Bonn, Germany. The main purpose was to describe long-term results and to provide prognostic factors for outcome with long-term overall survival as the primary endpoint.

In our analysis, median survival for the whole patient group was 17.1 months. However, large differences were seen between subgroups: For patients treated with up-front or consolidative HDT after achievement of a CR with conventional induction therapy as well as for patients with chemosensitive relapse, median OS has not been reached yet. OS for patients with an incomplete response to first-line chemotherapy still chemosensitive to salvage chemotherapy was 13.4 months. In contrast, patients with either chemoresistant relapse or primary refractory chemoresistant disease had no benefit from treatment with HDT followed by ASCT, achieving a median OS of less than 5 months.

Several groups have focused on the development of prognostic models capable of predicting outcome in patients with recurrent or refractory aggressive lymphoma. The most widely accepted prognostic factor is chemosensitivity to conventional dose second-line chemotherapy [24], [25]. Several additional factors like presence of bulky disease, three or more chemotherapy regimens prior to HDT, elevated LDH levels, short time to relapse, and high disease burden may also have some prognostic value [26], [27], [28], [29]. However, as a result of the inhomogeneous patient populations used to generate these models, no single prognostic model has achieved widespread acceptance in the setting of relapsed or refractory disease.

In our evaluation, only performance status and chemosensitivity were correlated with OS in univariate analysis with LDH baseline level reaching merely borderline significance. In multivariate analysis, only chemosensitivity remained to be of prognostic value. The small sample size of our trial limits the power of the statistical analysis.

Prince et al. tested the hypothesis that the amount of tumour burden - reflected by the remission status immediately prior to transplant - is an important prognostic indicator of survival for patients with aggressive lymphoma undergoing autologous transplantation for relapsed or refractory disease [28]. Patients with incomplete response to induction therapy or relapsed disease who achieved only a partial remission (PR) with conventional dose salvage chemotherapy had a markedly inferior outcome after subsequent HDT with ASCT than patients who were transplanted in complete remission (CR) state. In fact, remission status at transplant was the only factor predictive of outcome in this analysis. This finding is of particular importance, since it suggests the hypothesis that increasing the CR rate prior to transplant with improved conventional salvage therapies might translate into superior outcomes after HDT with ASCT for relapsed or refractory patients with aggressive NHL.

In this regard, we and others have recently reported on improved CR rates with the addition of the monoclonal antibody rituximab to conventional salvage regimens for relapsed or refractory NHL patients [30], [31], [32]. However, whether increasing the CR rate pre-transplant will finally translate into a significant survival advantage remains a critical question to be resolved in larger prospective trials with longer follow-up [33].

Special attention should be given to those patients with primary refractory disease or chemorefractory relapse. The role of HDT followed by ASCT for these patients has not been defined because there have been no randomised trials in this group of patients to date. Furthermore, the prognostic importance of chemosensitivity in the existing studies is biased by the inclusion of patients with various histologic diagnoses, the lack of chemosensitivity determination and - in particular - the different applied definitions for “refractory disease”. Thus, notwithstanding the limitations of our evaluation due to its small number of patients, a strength of this analysis might be the differentiated categorization of patients in terms of their disease status and grade of chemosensitivity.

Studies on HDT with ASCT for patients with induction failure – i.e. non-achievement of a CR to conventional induction chemotherapy – have reported progression-free-survival rates of 27%-69% [4], [34], [35], [36], [37]. The largest available data set of patients with diffuse aggressive NHL undergoing autologous transplantation after not achieving CR with induction chemotherapy was

published by Vose et al. in 2001 [18]. Retrospective evaluation of the 184 records from the Autologous Blood and Marrow Transplant Registry demonstrated 5-year probabilities of PFS and OS of 31% and 37%, respectively. Patients who remained chemotherapy-sensitive, had a good performance status, were younger than 55 years of age, had received only one or two prior chemotherapy regimens, and had received either pre- or post-transplant involved-field irradiation, did benefit most from this approach. Consequently, HDT has been accepted by many physicians for the treatment of patients with primary refractory disease provided that chemotherapy sensitivity is documented after salvage chemotherapy. These results have been confirmed in a Spanish retrospective analysis of 114 patients who failed to achieve a CR with 1st-line induction chemotherapy and received HDT/ASCT as part of their salvage treatment [37]. The 60% 3 year OS rate in patients with chemosensitive relapsed disease in our series is well in line with the results reported by the above mentioned trials with 45%-60% of patients achieving long-term survival.

In contrast, the outcome of patients with "truly" chemorefractory disease is very poor. Five-year survival rates are only about 10% in almost all published reports [19], [29], [38], [39], [40]. In the PARMA trial, 18 patients not responding to two courses of dexamethasone/high-dose ara-C/cisplatin (DHAP) received HDT followed by autologous bone marrow transplantation (ABMT). Of note, at least for patients with a low risk IPI score, a significant survival benefit was found in transplanted patients compared to the 70 remaining patients not undergoing HDT/ASCT [41]. Very recently, Glossmann et al. reported on their experiences with tandem transplantation in patients with primary progressive or relapsed lymphoma refractory to salvage treatment [42]. Tandem HDT followed by ASCT offered a small chance for cure at least for some patients in their series, leading the authors to conclude that patients lacking chemosensitivity should not a priori be excluded from transplant procedures. This is in particular true for younger patients, who are often willing to take the high risk of treatment failure as there might be a small chance for long-term survival.

The results of a very recently published retrospective analysis of 57 out of 425 relapsed or refractory lymphoma patients (17 Hodgkin's disease, 26 aggressive NHL, 14 indolent NHL) who received a second salvage regimen after failure of the first salvage regimen are helpful to more precisely assess the relevance of chemosensitivity in the treatment of aggressive NHL: From 15 patients with SD following first salvage therapy, five patients (33%) achieved a response to second salvage chemotherapy as opposed to only one of 24 (4%) patients with PD after first salvage treatment [21]. The 3-year estimated survival was 25% in the former group as opposed to only 4% in the latter group (the only patient who survived longer than 3 years in this group had indolent lymphoma). These observations are well in line with our experiences: All patients with PD to salvage chemotherapy died in less than eight months after HDT/ASCT. Thus, our results support the view that patients who undoubtedly show PD after conventional salvage therapy should generally not be offered HDT with ASCT since these patients do not benefit from this treatment approach.

# Conclusions

In summary, our results confirm that HDT and ASCT is a highly effective therapy leading to long-term survival in a substantial proportion of non-selected patients with DLBCL. In our series, high-risk patients receiving HDT followed by ASCT as part of their 1$^{st}$-line therapy, patients with incomplete response to conventional first-line therapy but chemosensitive disease as well as patients with chemosensitive relapse achieve high remission rates with the majority having a good long-term prognosis. In contrast, patients with primary refractory chemoresistant disease and patients with relapsed disease lacking chemosensitivity do not benefit from HDT with ASCT and should be candidates for either treatments with palliative intent or experimental approaches.

# Notes

## Conflicts of interest

None declared.

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