High-dose chemotherapy followed by autologous stem cell transplantation as first-line therapy in aggressive non-Hodgkin's lymphoma: a meta-analysis

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Background and Objectives. High-dose chemotherapy followed by autologous stem cell transplantation (HDT/ASCT) has proven to be superior to conventional chemotherapy in patients with chemosensitive relapse of aggressive non-Hodgkin's lymphoma (NHL). Therefore, HDT/ASCT was evaluated as part of first-line therapy. Several trials generated conflicting results. This meta-analysis summarizes the available evidence from all suitable studies.

Design and Methods. Prospective, randomized trials with HDT/ASCT as first-line therapy of aggressive lymphoma were included in this meta-analysis. The primary outcome was overall mortality. Statistical analysis applied the odds ratio (OR) and a fixed effects model.

Results. Eleven trials with 2228 patients were eligible for meta-analysis. Overall mortality was comparable in the HDT/ASCT and in control arms (OR=0.97, 95% CI: 0.69;1.36, p=0.9), with statistically significant heterogeneity between the trials. To resolve this, we tried to identify variables that could explain this heterogeneity. Among a range of methodological, patient- or treatment-related factors, subgroups formed by the proportion of bulky disease in treated patients, the type of therapy prior to HDT/ASCT, the drop-out rate from the HDT/ASCT arm, and the presence of high or high-intermediate risk IPI showed significant benefit for any of the treatment modalities. However, such *post-hoc* subgroup analysis may be considerably influenced by random or systemic biases.

Interpretation and Conclusions. Overall, the analysis of published evidence reveals very heterogeneous results and no overall survival benefit. Therefore, HDT/ASCT cannot be recommended as standard first line treatment for patients with aggressive NHL. However, the exploratory analyses presented here may help to design new trials for this treatment modality.

Key words: high-dose chemotherapy, autologous stem cell transplantation, non-Hodgkin's lymphoma, meta-analysis.

Haematologica 2003; 88:1304-1315
http://www.haematologica.org/2003_11/1304.htm

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High-dose chemotherapy (HDT) followed by autologous bone marrow transplantation (ABMT) was shown to provide significant advantage regarding event-free and overall survival in patients with chemosensitive relapses of aggressive non-Hodgkin´s lymphoma (NHL) after conventional therapy in the PARMA study.[1] These results encouraged many investigators to apply HDT already as part of first-line therapy and indeed this approach generated promising results in phase I/II trials.[2,3] Subsequently, several prospective, randomized trials compared HDT to conventional therapy in patients with aggressive lymphoma, yielding conflicting results.[4-16] This meta-analysis attempts to summarize the results of these trials.

Methods

Search strategy

MEDLINE (PubMed version) was searched until March 2003. The free text search term was: (*NHL* OR *lymphoma*) AND (*aggressive* OR *high* OR *intermediate*) AND *high dose* AND *transplantation*. The publication type term was *Randomized Controlled Trial*. No other restrictions were applied.

Additionally, reference lists of all identified trials and of comprehensive reviews in the field were screened. The volumes of abstracts of the annual meetings of the American Society of Hematology (ASH), the European Haematology Association (EHA), and the American Society of Oncology (ASCO) were screened from 1995 to 2002.

Inclusion and exclusion criteria

For inclusion, trials had to be prospective and randomized with standard conventional chemotherapy in one arm compared to high-dose chemotherapy followed by autologous stem cell transplantation in the other arm, in first line therapy of patients with aggressive non-Hodgkin´s-lymphoma analogous to the current WHO classification. Trials not fulfilling the inclusion criteria were excluded. Trials exclusively comprising follicular lymphoma or lymphoblastic lymphoma were also excluded.

Extraction process

A structured form was used to extract relevant data from the trials. Extraction was performed completely independently by two reviewers. Disagreements were resolved by consensus. Reviewers were not blinded to

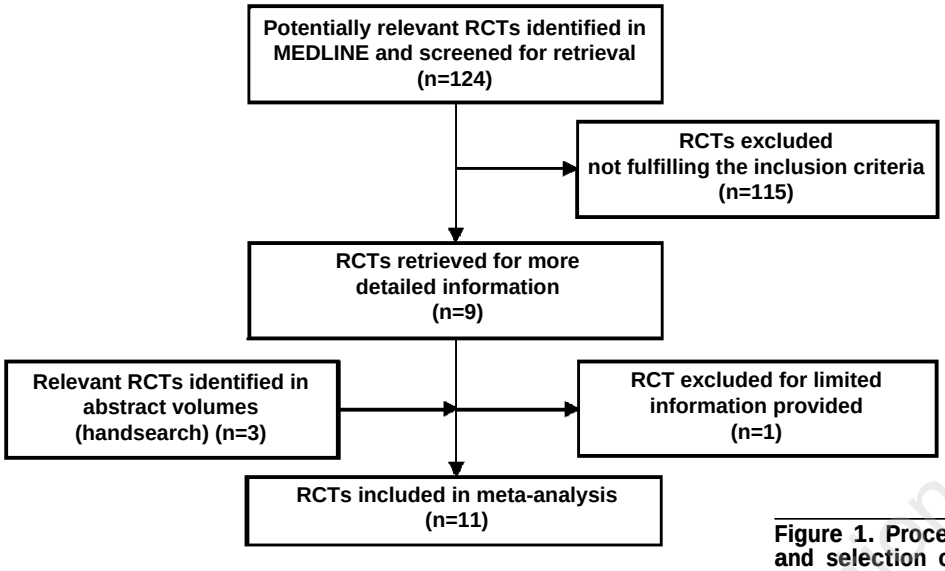

Figure 1. Process of identification and selection of relevant randomized, controlled trials according to the QUOROM statement.

authors or journals. Authors of publications only available as abstracts were contacted personally.

Definition of outcome

The pre-defined primary outcome was mortality of treated patients. Mortality was calculated from overall survival of patients as indicated in the reports.

Definition of subgroups

Subgroups were formed using the following criteria: (i) high-intermediate and high risk groups according to the International Prognostic Index (IPI);[17] (ii) induction therapy: (a) full course induction therapy was defined as a chemotherapeutic regimen comparable to at least six courses of CHOP or a CHOP-like standard regimen administered before high-dose therapy in the HDT/ASCT arm, (b) accordingly, less intensive or abbreviated chemotherapy before HDT/ASCT was considered shortened induction therapy, (c) upfront chemotherapy was regarded as a short high-dose sequential chemotherapy regimen followed by ASCT; (iii) response to induction therapy; (iv) proportion of diffuse large cell lymphoma: more or less than 60%; (v) proportion of T-cell lymphoma: more or less than 5%; (vi) total body irradiation as part of the protocol; (vii) involved field irradiation as part of the protocol; (viii) number of patients: more or less than 150 patients; (ix) start of recruitment: before or after 1993; (x) time of randomization: before the start or in the course of treatment; (xi) median age: more or less than 40 years; (xii) proportion of stage III/IV disease: more or less than 70% (xiii) proportion of ECOG performance status $\leq$2: more or less than 40%; (xiv) proportion of lactate dehydrogenase (LDH) elevation: more or less than 60%; (xv) proportion of extranodal sites involved: more or less than 30%; (xvi) proportion of bulky disease: more or less than 50%; (xvii) proportion of drop-out rate in the HDT/ ASCT arm: more or less than 25%; and (xviii) proportion of bone marrow involvement: more or less than 20%.

Statistical analysis

This meta-analysis was performed according to the guidelines of the Cochrane Collaboration and the QUOROM statement.[18] Statistical analyses were performed using Meta View/Review Manager 4.1 (The Cochrane Collaboration, accessed at *http://www.cochrane.de*) and Comprehensive Meta Analysis 1.0.23 (Biostat, Englewood, NJ, USA). The statistical effect parameter was the Odds Ratio (OR; risk calculated as the number of patients with a certain event divided by the number of patients without this event). It was analyzed with a fixed effect model. Analysis with a random effect model generated comparable results. Heterogeneity between the trials was assessed by the Mantel-Haenszel χ^2 test for heterogeneity, as calculated in Meta View/Review Manager 4.1 and Comprehensive Meta Analysis 1.0.23.

Results

Trials included

The process of identification and selection of the relevant randomized controlled trials (RCT) accord-

Table 1. Inclusion criteria of eligible trials.

Study	*Inclusion criteria*	*Inclusion criteria after induction therapy*
HOVON Verdonck *et al.* 1995	1. histology: intermediate, high grade (WF: D, E, F, G, H) 2. stages: II-IV 4. age: 15-60 years	PR (reduction 25-90%, w/o BM-infiltration)
Italian Multicenter, Martelli *et al.* 1996	1. histology: diffuse large cell (centroblastic and immunoblastic;WF: G,H), Burkitt's (WF: J), anaplastic large cell, pleomorphic T-cell (WF: unclassifiable) 2. stages: I mediastinal, II-IV 3. ECOG <3 4. age: 15-60 years	PR (reduction 50-80%)
GELA LNH 87-2 Haioun *et al.* 1994 Haioun *et al.* 1997 Haioun *et al.* 2000	1. histology: intermediate, high (WF) 2. at least one of following characteristics: ECOG performance status 2-4 or ≥ 2 extranodal sites or bulky disease or CNS-involvement or Burkitt/ lymphoblastic lymphoma w/o BM/CNS-involvement 4. age: < 55 years 5. IPI: all	CR
Milan Trial Gianni *et al.*1997	1. histology: diffuse large cell (WF: G), diffuse large cell immunoblastic (WF: H) w/o BM-involvement, excluded: T-cell phenotype 2. stages: I & II bulky, III, IV 3. ECOG performance status 0-4 4. age: 17-60 years	CR, PR (crossover when: PR < 80%, PD, relapse)
Italian NHL-CSG Santini *et al.* 1998	1. histology: intermediate and high grade according to WF (excluded: Burkitt, lymphoblastic lymphoma) w/o BM-infiltration 2. stages II bulky, III, IV 4. age: 15-60 years	Control: CR; HDT: CR, PR, NR
Italian Lymphoma Intergroup Vitolo *et al.* 2001	1. histology: diffuse large cell lymphoma (+/- BM involvement) 4. Age: 15-60 5. age-adjusted IPI ≥2	n.a.
EORTC Kluin Nelemans *et al.* 2001	1.histology: stages II-IV intermediate-grade (WF: D, E, F, G); stages I bulky, II-IV, diffuse large-cell immunoblastic, anaplastic large-cell, pleomorphic T-cell (large, small), angioimmunoblastic w/ dysproteinemia-like T-cell excluding lymphoblastic, Burkitt 3. WHO performance status ≤2 4. Age: 15-60 (increased to 65 years because of slow accrual) 5. IPI: all	CR, PR (w/o BM-involvement)
GELA LNH93-3 Gisselbrecht *et al.* 2002	1. histology: aggressive NHL (excluded: Burkitt's, lymphoblastic lymphoma w/meningeal and/or BM-involvement; PCNSL) 4. Age: 15-60 5. age-adjusted IPI ≥2	CR CRu (>75%) PR (50-75 %)
GHGLSG Kaiser *et al.* 2002	1. histology: primary aggressive NHL (Kiel classification), excluded: lymphoblastic lymphoma when age <35) 2. stages II-IV 3. LDH > normal 4. age: 18-60 years 5. IPI: all	CR, PR
5. IPI: all GOELAMS Milpied *et al.* 2002	1. grades: intermediate, high (73%: diffuse large cell histology) 2. stages: II bulky (abdominal), III, IV 4. age: 15-60 years 5. IPI: non high-risk	CR, PR
Italian Multicenter Martelli *et al.* 2003	1. histology: high grade lymphomas: diffuse large cell (B-phenotype), anaplastic large cell, peripheral T-cell lymphoma, other (5%) 2. stages: I bulky, II-IV 4. age: 15-60 years 5. age-adjusted IPI ≥2	CR, Cru, PR, MR

BM: bone marrow; CNS: central nervous system; CR: complete remission; CRu: unconfirmed complete remission; HDT: high dose therapy; IPI: international prognostic index; MR: minimal response; NR: no response; PCNSL:primary CNS lymphoma; PD: progressive disease; PR: partial remission; WF: Working Formulation; w/o: without.

Table 2. Therapy regimens of included trials.

Study	*Induction therapy*	*Control therapy*	*High dose therapy*	*Source of autologous transplant*
HOVON Verdonck *et al*. 1995	3×CHOP	5×CHOP	1×CHOP hd cyclophosphamide TBI 800cGy	BM
Italian Multicenter Martelli *et al*. 1996	4× F-MACHOP or 8× MACOP-B	6×DHAP	BEAC	BM
Milan Trial Gianni *et al*.1997	Δ	12× MACOP-B (+/- radiotherapy)	AVP hd cyclophosphamide methotrexate + vincristine etoposide a) TBI + melphalan b) mitoxantrone + melphalan	PBSC/BM
Italian NHL-CSG Santini *et al*. 1998	12×VACOP-B	CR: follow-up PR/NR: DHAP +/- radiotherapy (IF)	BEAM	BM
GELA LNH 87-2 Haioun *et al*. 1994 Haioun *et al*. 1997 Haioun *et al*. 2000	4×ACVBP (NCVBP)	2× methotrexate 2× ifosfamide + etoposide 1× L-asparaginase 2× cytosine-arabinoside	2x methotrexate CBV	BM
Italian Lymphoma Intergroup Vitolo *et al*. 2001	Δ	6× megaCEOP (BM+: 8×)	Debulking: APO hd cyclophosphamide, methotrexate, vincristine, etoposide (BM+ → DHAP) mitoxantrone, melphalan	PBSC
EORTC Kluin-Nelemans *et al*.	3×CHVmP/BV	5x CHVmP/BV (+ radiotherapy in: PR, CR with initial diameter >5 cm, macroscopically residual disease after 3 cycles)	3×CHVmP/BV BEAC	BM
GELA LNH93-3 Gisselbrecht *et al*. 2002	Δ	4×ACVBP + MTX i.th. 2x methotrexate 4×etoposid, ifosfamide 2×cytosine-arabinoside	1×CEOP + MTX i.th. 2×ECVBP BEAM	PBSC
GHGLSG Kaiser *et al*. 2002	Δ	5×CHOEP (+ involved field radiotherapy)	3×CHOEP BEAM (+ involved field radiotherapy)	PBSC/BM
GOELAMS Milpied *et al*. 2002	Δ	8x CHOP	2×CEEP MTX, cytosine-arabinoside BEAM	PBSC
Italian Multicenter Martelli *et al*. 2003	Δ	12×MACOP-B (± radiotherapy [bulky])	8×MACOP-B BAVC (± radiotherapy [bulky])	PBSC

ACVB: Doxorubicin, Cyclophosphamide, Vinblastine, Bleomycin; ACVBP: Doxorubicin, Cyclophospahmide, Vindesine, Bleomycin, Prednisone; APO = AVP: Doxorubicin, Prednisone, Vincristine BAVC: Carmustine, Cytosine-Arabinoside, Etoposide, Cyclophosphamide; BEAC: Carmustin, Etoposide, Cytosine-Arabinoside, Cyclophosphamide; BEAM: Carmustin, Etoposide, Cytosine-Arabinoside, Melphalan; BM: Bone marrow; CBV: Cytoxantrone; BCNU, Etoposide; CEEP: Cyclophosphamide, Epirubicin, Vindesine, Prednisone; CEOP: Cyclophosphamide, Epirubicin, Vincristine, Prednisone; CHOP: Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; CHOEP:Cyclophosphamide, Doxorubicin, Vincristine, Etoposide, Prednisone; CHVmP/BV: Cyclophosphamide, Doxorubicin, Teniposid, Prednisone, Bleomycin, Vincristine; DHAP: Dexamethasone, Cytosine-Arabinoside, Cisplatin; ECVBP:Epirubicin, Cyclophosphamide, Vindesine, Bleomycin, Prednisone; F-MACHOP: 5-Fluorouracil, Folinic Acid, Methotrexate, Cytosine-Arabinoside, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; hd: high dose; MACOP-B: Methotrexate, Doxorubicin, Cyclophosphamide, Vincristine, Prednisone, Bleomycin; MTX: Methotrexate; NCVB: Mitoxantrone, Cyclophosphamide, Vinblastine, Bleomycin; PBSC:peripheral blood stem cells; TBI: total body irradiation; VACOP-B: Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Prednisone, Bleomycin.

Table 3. Outcome of all included trials.

Overall Study	Patients		MOT	Overall survival	
	HDT+ ASCT	Control		HDT+ ASCT	Control
HOVON Verdonck *et al.* 1995	34	35	48 mo.	56%	85%
Italian Multicenter Martelli *et al.* 1996	22	27	40 mo.	73%	59%
Milan Trial Gianni *et al.* 1997	48	50	55 mo.	81%	55%
Italian NHL-CSG Santini *et al.* 1998	63	61	42 mo.	65%	65%
GELA LNH 87-2 Haioun *et al.* 1994/1997/2000	268	273	54 mo.	69%	67%
ILI Vitolo *et al.* 2001	60	64	36 mo.	60%	51%
EORTC Kluin-Nelemans *et al.* 2001	98	96	53 mo.	68%	77%
GELA LNH93-3 Gisselbrecht *et al.* 2002	189	181	60 mo	46%	60%
GHGLSG Kaiser *et al.* 2002	158	154	46 mo.	62%	63%
GOELAMS Milpied *et al.* 2002	98	99	48 mo.	71%	55%
Italian Multicenter Martelli *et al.* 2003	75	75	55 mo.	65%	65%

MOT: median observation time. ILI: Italian Lymphoma Intergroup

Table 4. Outcome of included trials according to high-intermediate / high IPI.

Overall Study	Patients		MOT	Overall survival	
	HDT+ ASCT	Control		HDT+ ASCT	Control
Italian NHL-CSG Santini *et al.* 1998	34	36	42 mo.	68%	55%
GELA LNH 87-2 Haioun *et al.* 2000	125	111	96 mo.	64%	49%
ILI Vitolo *et al.* 2001	60	64	36 mo.	60%	51%
GELA LNH93-3 Gisselbrecht *et al.* 2002	189	181	60 mo.	46%	60%
GHGLSG Kaiser *et al.* 2002	112	113	46 mo.	56%	50%
GOELAMS Milpied *et al.* 2002	56	49	48 mo.	74%	44%
Italian Multicenter Martelli *et al.* 2003	75	75	55 mo.	65%	65%

MOT: median observation time. ILI: Italian Lymphoma Intergroup

ing to the QUORUM statement is depicted in Figure 1. Eleven trials were identified, reporting on the overall survival of 2228 patients (1113 patients treated with HDT/ASCT, and 1115 control patients). Nine trials are available as fully published

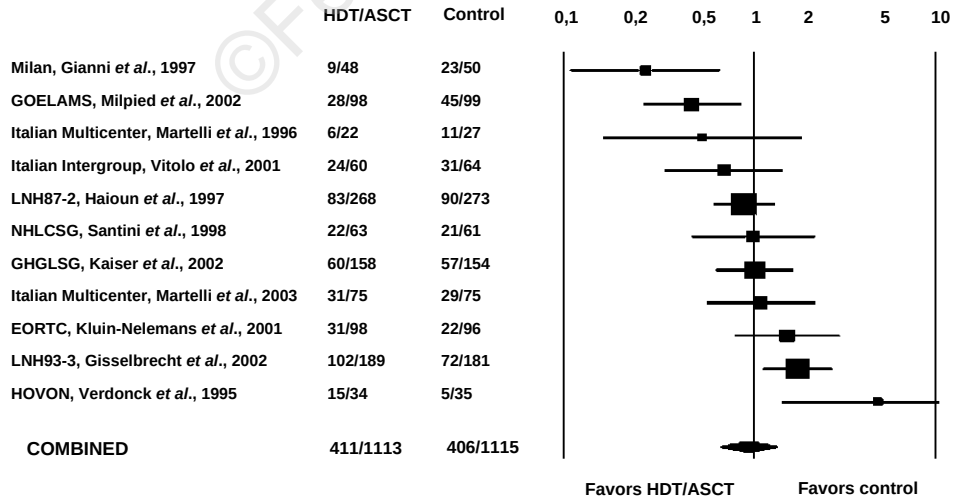

Figure 2. Summary of all eligible trials.

Table 5. Subgroups according to patient and study characteristics.

References	*#15 1995*	*#12 1996*	*#5 1997*	*#14 1998*	*#7,8,9 1994-1997-2000*	*#11 2001*	*#16 2001*	*#6 2002*	*#10 2002*	*#13 2002*	*#4 2003*
Study characteristics											
TBI applied	+	–	+	–	–	–	–	–	–	–	–
Involved field radiation applied	–	–	+	+	–	+	–	–	+	–	+
Patient number <150	+	+	+	+	–	–	+	–	–	–	–
Start of recruitment before 1993	+	+	+	+	+	+	–	–	+	–	–
Randomization after start of treatment	+	+	–	–	+	+	–	–	–	–	–
Drop out rate in HDT/ASCT- arm <25%	+	+	+	–	–	–	+	–	–	+	–
Patient characteristics											
Diffuse large cell lymphoma <60%	+	+	–	+	+	+	O	–	+	–	–
T cell Lymphoma <5%	+	–	+	–	–	+	O	–	+	+	–
Median age <40 years	–	+	+	–	+	–	–	–	–	–	+
Stage III/IV <70%	+	+	–	+	+	+	–	–	+	–	–
ECOG ≥2 <40%	+	O	–	+	+	O	–	–	+	O	–
LDH elevation <60%	–	+	–	–	+	+	–	–	+	+	–
Extranodal involvement ≥2 <30%	+	O	–	+	+	+	+	–	–	O	O
Bulky disease <50%	–	–	–	–	–	+	+	+	–	O	+
Bone marrow involvement <20%	+	+	+	+	–	+	–	–	–	–	+

papers,[4–12,14,15] whereas two trials are published only as abstracts.[13,16] Table 1 shows the inclusion criteria of each study regarding histology, age, stage of disease, performance status, and (age-adjusted) IPI. Furthermore, the remission status after induction therapy required for randomization is mentioned. Table 2 gives an overview of the different therapeutic regimens administered in the studies, listed by induction therapy and post-induction therapy in the control arm and HDT/ASCT arm, respectively. The source of the hematopoietic stem cells is also detailed. Table 3 summarizes the number of patients included in the control and HDT/ASCT arms, and the overall survival rates at the median time of follow-up. Table 4 indicates the outcome of patients with intermediate/high-intermediate IPI. A funnel plot, calculated with Meta View/Review Manager 4.1, was symmetric (data not shown), indicating that no significant publication bias was detectable.

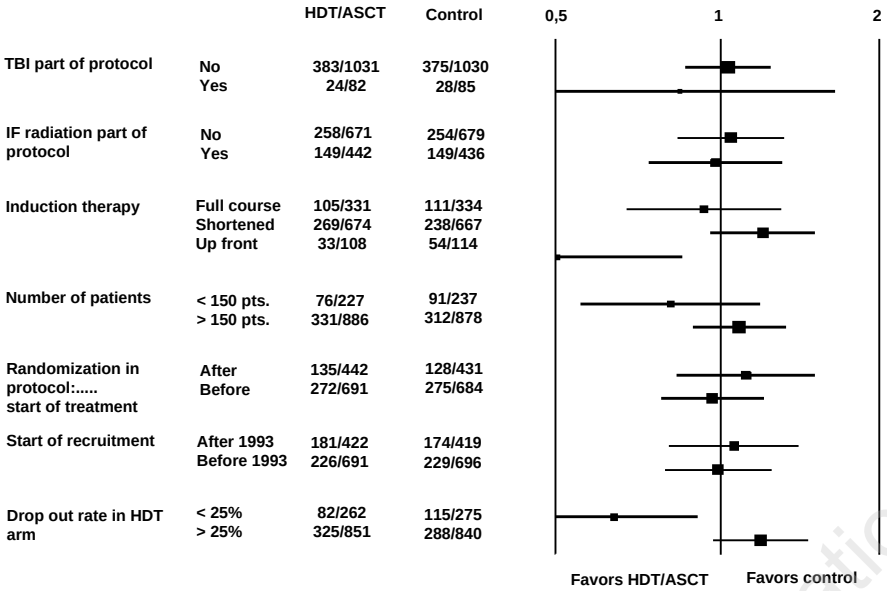

Figure 3. Subgroup analysis according to protocol / study characteristics.

Overall mortality

Figure 2 displays the results of all trials for overall survival. The vast disparity of results with trials demonstrating benefit or significant harm of HDT/ASCT, leads to a statistically significant heterogeneity among the trials (χ^2=33, p=0.0003). During the observation period of the trials, 411/1113 patients (36.9%) who had received HDT/ASCT, and 406/1115 patients (36.4%) in the control arms died (OR=1.02, CI 95%=0.86;1.21, p=0.8). A meta-regression analysis to explain this great heterogeneity was performed with the variables displayed in Table 5, but demonstrated significant influences only for induction therapy when shortened induction therapy was compared to pooled results of full course induction therapy and up front HDT/ASCT.

Subgroup analysis.

Protocol As described in the methods section, studies were summarized in subgroups according to a cut off value regarding certain characteristics. Subgroup analysis was performed according to a variety of criteria (Table 5). Among the determined protocol characteristics (Figure 3), the date of starting recruitment, the number of patients included, the time of randomization in the course of the protocol, and the application of total body or involved field irradiation to patients did not identify a study characteristic responsible for a significant advantage or disadvantage of HDT/ASCT over the control therapy. Differences were identified when studies were evaluated according to the intensity of treatment before HDT/ASCT. There were two studies in which full course induction therapy was administered to 665 included patients before HDT/ASCT.[7,14] Overall mortality was comparable in the HDT/ASCT arms (105/331, 31.7%) and the control arms (111/334, 33.2%). The OR favored neither of the two therapy regimens (0.93 [0.67;1.29], p=0.7). In the subgroup of studies applying shortened induction therapeutic regimens (1341 patients) there was a trend towards an advantage (1.19 [0.96;1.49], p=0.12) for the control therapies (mortality 238/667 [35.7%]) over HDT/ASCT (mortality 269/674 [39.9%]). A significant advantage from HDT/ASCT over control therapy was seen in the subgroup of two studies[5,16] (228 patients) using high-dose sequential chemotherapy before a myeloablative regimen followed by hematopoietic stem-cell support: mortality in the HDT patients (33/108, 30.1%) was lower than that in the control patients (54/114, 47.4%). The odds ratio indicates a significant advantage from the HDT/ASCT treatment (0.49[0.28;0.85], p=0.01).

Another interesting observation can be made from examining subgroups of studies according to whether the drop-out rate of patients was more or less than 25%: in five studies[5,12,13,15,16] (537 patients) actually administering therapy to more than 75% of patients randomized in the HDT/ASCT arm, there was a significant advantage (0.63 [0.44; 0.90], p=0.01) of HDT/ASCT (82/262, 31.3%) over control therapy (115/275, 41.8%). In the remaining six studies[4,6,7,10,11,14] (1691 patients) with a drop-out out rate of more than 25%, there was a trend towards a significant advantage (1.18 [0.97;1.44], p=0.095) of control therapies (325/851, 38.2%) over HDT/ASCT (288/840, 34.3%). There was significant heterogeneity between these two subgroups (χ^2=9.1, p=0.0026).

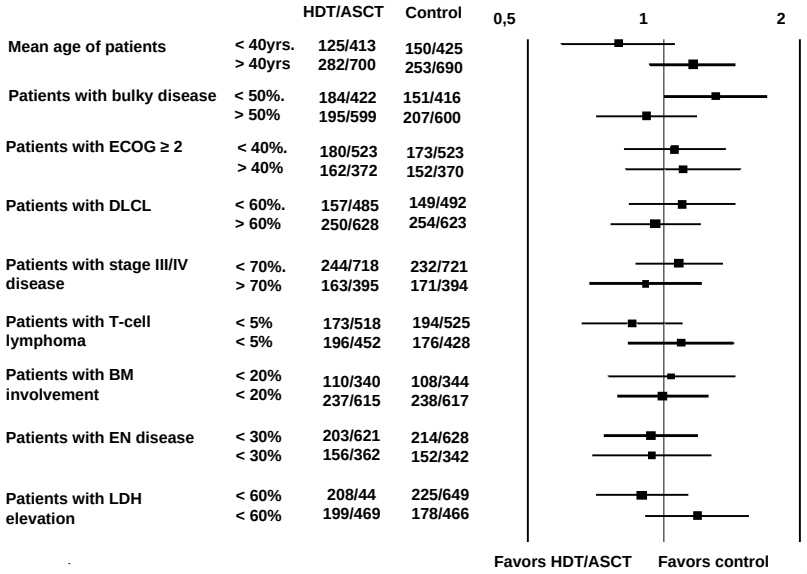

Figure 4. Subgroup analysis according to patients' characteristics.

Subgroup analysis. Patient's characteristics

Subgroups were formed according to certain characteristics of the patients when they were given in an appropriate number of studies (Table 5, Figure 4). No advantage for any treatment modality was shown with respect to the proportion of patients with diffuse large cell lymphoma, the proportion of patients with T-cell lymphomas, proportion of patients with stage III/IV disease, the proportion of patients with an ECOG performance status ≥ 2, the proportion of patients with bone marrow involvement, the proportion of patients with elevated LDH, and the proportion of patients with ≥2 extranodal sites.

When the mean age of patients was less than 40 years[4,5,7,12] (838 patients), mortality was only 30.3%

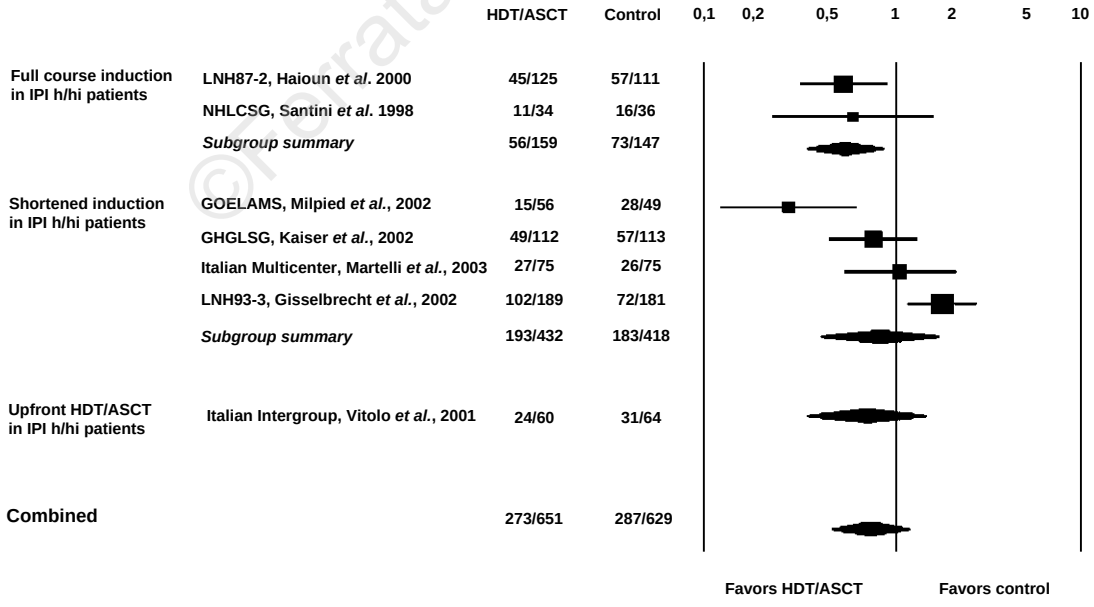

Figure 5. Subgroup analysis according to induction therapy and IPI.

(125/413) for patients treated with HDT/ASCT, as compared to 35.3% (150/425) in the control arm (0.80[0.60,1.06], p=0.12). Contrariwise, when the mean age of patients was more than 40 years[6,10,11,13-16] (1390 patients), there was an advantage (1.17;[0.94;1.45], p=0.16) for control therapies (36.7%, 253/690) over HDT/ASCT (40.3%, 282/700). Both subgroups showed no statistically significant results. However, there was significant heterogeneity between both age groups (χ^2=4.29, p=0.038).

When bulky disease was present in less than 50% of the patients[4,6,11,16] (838 patients), control therapies (151/416, 36.3%) achieved signficantly better results (OR 1.31[1.01;1.70], p=0.042) than HDT/ASCT (184/422, 43.6%). When bulky disease was present in more than 50% of patients, there was no significant difference between the two different treatment modalities. Again, there was significant heterogeneity (χ^2=4.06, p=0.044) between these two subgroups.

We also formed a subgroup of seven studies (1280 patients) regarding the International Prognostic Index (Figure 5). There was an advantage (0.92[0.73;1.14] for high-intermediate and high risk patients treated with HDT/ASCT (41.3%, 273/651) over those patients treated with control therapies (45.6%, 287/629), although the difference was not statistically significant (p=0.4). Four of these seven studies[4,6,10,13] (850 patients) applied HDT/ASCT after shortened induction therapy. The mortality rate was 44.7% (193/432) in the HDT/ASCT arm, and 44.3% (185/418) in the control arm, with no significant advantage for any treatment (OR 1.02 [0.78;1.33], p=0.8). Subgroup analysis of the data supplied in those two studies[9,14] (306 patients) applying full course induction therapy before HDT/ASCT showed no heterogeneity (χ^2=0.05, p=0.84). Here, overall mortality was 35.2% (56/159) and 49.7% (73/147) in the HDT/ASCT patients and in the control patients, respectively. The advantage for HDT/ASCT in this subgroup was statistically significant according to the OR (0.55[0.35;0.87], p=0.01). Additionally, there was a statistically significant heterogeneity (χ^2=5.08, p=0.024) between the two subgroups.

Discussion

The superiority of HDT followed by ASCT compared to standard salvage therapy was clearly demonstrated in a single randomized trial in patients with first chemosensitive relapse of aggressive NHL.[1] On the basis of the results of this trial, HDT/ASCT was established as standard therapy in such patients. This approach suggested the possibility of improving the outcome of patients by adding HDT/ASCT to first-line therapy. Although several phase I/II trials supported the use of this strategy,[2,3] results of larger, prospective randomized trials have been contradictory, and many investigators' expectations have not been fulfilled. Nevertheless, interim and retrospective analyses of some trials revealed subsets of patients obviously profiting from HDT/ASCT in terms of progression-free and overall survival.

This meta-analysis reviews the published evidence concerning HDT/ASCT in first line therapy of patients with aggressive NHL drawn from eleven trials including 2228 patients. However, the results of these trials are profoundly heterogeneous and cannot easily be aggregated. Most probably, this heterogeneity reflects the very diverse designs of the trials. The comparison of the published data is particularly hampered by the following problems: (1) there was a great variety of therapeutic regimens, both among standard and high dose therapies; (2) some studies applied HDT as part of front-line therapy after shortened induction therapies, others used HDT as consolidation therapy after full course induction therapy; in two studies HDT was administered *up-front*; (3) trials had different remission status requirements for HDT/ASCT; (4) trials included varying proportions of patients with different histological disease subtypes; (5) the patients' characteristics were different (Tables 1 and 2).

For example, only two trials administered an induction therapy based on CHOP; only four trials used BEAM as the conditioning regimen (Table 2). The inclusion criteria also differed widely (Table 1). Some trials only selected patients in complete remission, whereas others explicitly excluded these patients.

From the current standpoint, it is regrettable that the published data are poorly comparable. Investigators obviously planned their trials based on different theories and local preferences without coordination with other investigators. To overcome these shortcomings, this meta-analysis attempts to summarize the previous evidence within its methodological limits, in order to give new trials a better chance of choosing an effective treatment for the appropriate group of patients.

We analyzed several variables that could have influenced the results. Selection of criteria to identify appropriate patients for front-line HDT/ASCT required formation of well-defined categories. These had to be applicable to the majority of the selected trials. Furthermore, published data had to provide sufficient and detailed information for the subgroup analysis. Meta-regression calculated on these underlying data only identified short induction therapy, when compared to full course induction therapy and up-front HDT/ASCT, as an explanation of the heterogeneity of results.

The remission status of patients before HDT/ASCT differed widely between the analyzed trials. It has

been suggested that the speed of achieving a CR during front-line therapy is of major prognostic relevance (patients responding very quickly to front-line therapy seem to have a more favorable outcome). In two trials, HDT/ASCT was administered to slowly or incompletely responding patients (i.e. patients in whom CR was not achieved) with conflicting results.[12,15] The purpose of these studies was to determine the potency of HDT/ASCT in improving the prognosis of these patients for whom the outcome is generally poor by achieving higher CR rates through early intensification of front-line therapy. In this analysis, no advantage for HDT/ASCT could be demonstrated. But, both the HOVON[15] and the Martelli[12] trial have limitations because of their small sample size. Concern has also been expressed with regard to the HOVON study, because the treatment arms included different percentages of patients with specific subtypes of aggressive NHL. Finally, another problem of both studies was the impossibility of distinguishing complete responders with residual masses from partial responders with persistent viable tumors using only standard radiographic criteria. Thus, additional studies are clearly needed to define the role of HDT in this subset of patients.

Analysis of six other trials administering HDT/ASCT to all responding patients (i.e. patients with CR or PR) after induction therapy also showed no significant benefit of HDT/ASCT compared to conventional chemotherapy. Even one large trial that randomized only those patients to further consolidating therapy who had achieved CR after full course standard therapy failed to show that this strategy was an improvement over conventional therapy.[9] Therefore, the remission status of patients after induction therapy alone does not allow a general statement to be made on whether HDT/ASCT is superior to conventional chemotherapy.

The most promising parameter for identifying patients with a poor prognosis is the IPI, which assigns patients to four different risk-groups (low, low-intermediate, high-intermediate and high).[17] In some trials applying this index retrospectively, patients with high-intermediate and high-risk profiles had significantly better results with HDT/ASCT than those treated with conventional chemotherapy.[9,14,19-21] As a consequence, more recently designed trials prospectively evaluated the effect of HDT/ASCT in consideration of the IPI.[4,6,16] Overall, the results of these trials were not able to demonstrate a significant benefit for HDT/ASCT in the high and high-intermediate subgroup. However, further subgroup-analysis with the focus on induction therapy before HDT/ASCT revealed an interesting point. Whereas no statistically significant difference could be demonstrated between the HDT/ASCT and conventional chemotherapy groups in patients given shortened induction therapy,[4,6,10,11,13] significantly superior results were achieved by high-dose consolidation therapy in those trials in which full course induction therapy was administered (Figure 5).[9,14]

Within the group of studies administering shortened induction therapy, one trial even had to be stopped because of a statistically significant advantage for the control group.[6] On the other hand, there is a remarkable study showing a significant benefit for HDT/ASCT.[13] Two aspects are noteworthy in this trial: (1) only high-intermediate risk patients were included; (2) following a dose-intensive shortened induction therapy (two courses of CEEP), another intensive consolidating therapy was administered. These two facts presumably contribute to the low drop-out rate with regard to the planned HDT/ASCT of only 15%; the documented drop-out rates from other studies were reported to be up to 35%.[4,6,10]

It must be kept in mind that the countenancing results reported by Haioun *et al.*[7] had been achieved in a highly selected patient population: only patients in CR after standard chemotherapy were randomized to either HDT/ASCT or conventional therapy. Although the LNH87-2 is the largest trial published so far and included 916 patients with aggressive NHL, as a result of the strict inclusion criteria, only 30.2% of patients (277/916) were actually randomized. Ongoing trials, such as the North American S9704, comparing HDT/ASCT after full course induction therapy with conventional standard therapy, will provide additional information in the near future.

Two trials have been investigating the role of HDT/ASCT as part of an intensified induction treatment, i. e. *up-front* HDT/ASCT: Gianni *et al.*[5] introduced a sequential high-dose chemotherapeutic regimen followed by ASCT after either total body irradiation/melphalan or mitoxantrone/melphalan. The results of HDT/ASCT were superior to those of standard conventional therapy. In another trial administering the same therapeutic regimen to high-intermediate and high risk patients, these encouraging results have not been confirmed so far.[16] Subgroup analysis of these two trials shows an odds ratio with significant advantage for HDT/ASCT. However, only a small number of patients received this regimen. Therefore, the results of the European Mistral trial, evaluating the value of an up-front HDT/ASCT regimen in a large prospective trial, are awaited with great interest. The German High Grade Lymphoma Study Group has recently initiated another approach by evaluating the role of a sequential HDT/ASCT regimen applying three courses of MegaCHOEP.[22]

In addition to patient selection discussed earlier, a crucial point of all meta-analyses is the varying follow-up period of the studies included. The average observation time reported by the trials included in this analysis was 48.8 months (Table 3). It is

clear from the Kaplan-Meier plots in all trials published as full papers that a plateau is reached after an adequate follow-up period. Thus, in the majority of trials, the results may be regarded as mature.

From our analysis, it seems that high-intermediate and high risk patients treated with full-course induction therapy before HDT/ASCT may have a better outcome than similar patients treated with control therapies. Additionally, the absence of bulky disease and an age younger than 40 years seem to favor HDT/ASCT over conventional control therapies. However, we must explicitly state that caution is highly advisable when interpretating *post-hoc* subgroup analyses. These cannot be used for recommendations on treatment selection for individual patients. Nevertheless, with appropriate care, they can be used in the development of new, empirically based research hypotheses.

What conclusions can be drawn with respect to the design of future trials? Overall, the results may support the hypothesis that HDT/ASCT is superior in terms of OS in high and high-intermediate risk patients when this strategy is used after maximum tumor reduction has been achieved. As aggressive lymphoma is a fast proliferating disease early treatment delays may be detrimental and this could explain the possible advantage of studies administering HDT/ASCT only after complete induction therapy has been applied. Accordingly, trials administering HDT/ASCT as part of up-front therapy also achieved good results. An alternative hypothesis, however, is that the superior results achieved with HDT/ ASCT are due to a selection of *good-risk* patients as the others have already relapsed before the strategy can be applied. Detailed analysis of Kaiser's study revealed that most failures in the HDT/ASCT arm occurred before the actual administration of this therapeutic modality and were possibly due to the delayed application of the intended therapy.

In this meta-analysis, we have shown that there is an advantage for HDT/ASCT over conventional control therapies when the drop-out rate of patients from the HDT/ASCT treatment arm is less than 25%. As a practical consequence, timely and dose-intensive treatment is essential in aggressive lymphoma. An important goal, particularly for the group of high-risk patients according to the IPI, must be the avoidance of treatment failure before high-dose chemotherapy by applying dose-intensive chemotherapy in the early phase of treatment. Every effort should be made to prevent treatment delays in high-risk patients.

In summary, the relevance of HDT followed by ASCT in first line therapy of aggressive NHL has still not been conclusively demonstrated. Given the recent improvements of conventional chemotherapeutic regimens, only new large, well-performed clinical trials, which take into account the experiences summarized in this meta-analysis, will be able to define the future role of HDT/ASCT.

References

1. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995;333:1540-5.
2. Nademanee A, Schmidt GM, O'Donnell MR, Snyder DS, Parker PA, Stein A, et al. High-dose chemoradiotherapy followed by autologous bone marrow transplantation as consolidation therapy during first complete remission in adult patients with poor-risk aggressive lymphoma: a pilot study. Blood 1992;80:1130-4.
3. Freedman AS, Takvorian T, Neuberg D, Mauch P, Rabinowe SN, Anderson KC, Soiffer RJ, et al. Autologous bone marrow transplantation in poor-prognosis intermediate-grade and high-grade B-cell non-Hodgkin's lymphoma in first remission: a pilot study. J Clin Oncol 1993;11:931-6.
4. Martelli M, Gherlinzoni F, De Renzo A, Zinzani PL, De Vivo A, Cantonetti M, et al. Early autologous stem-cell transplantation versus conventional chemotherapy as front-line therapy in high-risk, aggressive non-Hodgkin´s lymphoma: an Italian multicenter randomized trial. J Clin Oncol 2003; 21:1255-62.
5. Gianni AM, Bregni M, Siena S, Brambilla C, Di Nicola M, Lombardi F, et al. High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. N Engl J Med 1997;336:1290-7.
6. Gisselbrecht C, Lepage E, Molina T, Quesnel B, Fillet G, Lederlin P, et al. Shortened first-line high-dose chemotherapy for patients with poor-prognosis aggressive lymphoma. J Clin Oncol 2002;20:2472-9.
7. Haioun C, Lepage E, Gisselbrecht C, Bastion Y, Coiffier B, Brice P, et al. Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor-risk aggressive non-Hodgkin's lymphoma: updated results of the prospective study LNH87-2. Groupe d'Etude des Lymphomes de l' Adulte. J Clin Oncol 1997;15:1131-7.
8. Haioun C, Lepage E, Gisselbrecht C, Coiffier B, Bosly A, Tilly H, et al. Comparison of autologous bone marrow transplantation with sequential chemotherapy for intermediate-grade and high-grade non-Hodgkin's lymphoma in first complete remission: a study of 464 patients. Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1994;12:2543-51.
9. Haioun C, Lepage E, Gisselbrecht C, Salles G, Coiffier B, Brice P, et al. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol--a groupe d'Etude des lymphomes de l'Adulte study. J Clin Oncol 2000;18:3025-30.
10. Kaiser U, Uebelacker I, Abel U, Birkmann J, Trumper L, Schmalenberg H, et al. Randomized study to evaluate the use of high-dose therapy as part of primary treatment for "aggressive" lymphoma. J Clin Oncol 2002;20:4413-9.
11. Kluin-Nelemans HC, Zagonel V, Anastasopoulou A, Bron D, Roozendaal KJ, Noordijk EM, et al. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomized phase III EORTC study. J Natl Cancer Inst 2001;93:22-30.
12. Martelli M, Vignetti M, Zinzani PL, Gherlinzoni F, Meloni G, Fiacchini M, et al. High-dose chemotherapy followed by autologous bone marrow transplantation versus dexamethasone, cisplatin, and cytarabine in aggressive non-Hodgkin's lymphoma with partial response to front-line chemotherapy: a prospective randomized Italian multicenter study. J Clin Oncol 1996;14:534-42.
13. Milpied N, Deconninck E, Colombat P, Ifrah N, Delwail V, Berthou C, et al. Frontline high-dose chemotherapy (HDC) with autologous stem cell transplantation vs standard CHOP regimen for patients (pts) (<=60 yo) with non IPI high risk intermediate or high grade lymphomas (NHL). Final results of a randomized trial by the GOELAMS. Blood 2002;100:

180a[abstract].
14. Santini G, Salvagno L, Leoni P, Chisesi T, De Souza C, Sertoli MR, et al. VACOP-B versus VACOP-B plus autologous bone marrow transplantation for advanced diffuse non-Hodgkin's lymphoma: results of a prospective randomized trial by the non-Hodgkin's Lymphoma Cooperative Study Group. J Clin Oncol 1998;16:2796-802.
15. Verdonck LF, van Putten WL, Hagenbeek A, Schouten HC, Sonneveld P, van Imhoff GW, et al. Comparison of CHOP chemotherapy with autologous bone marrow transplantation for slowly responding patients with aggressive non-Hodgkin's lymphoma. N Engl J Med 1995;332:1045-51.
16. Vitolo U, Liberati AM, Deliliers GM, Calvi R, Baldini L, Bertini M, et al. A multicenter randomized trial by the Italian Lymphoma Intergroup (ILI) Comparing high dose chemotherapy (HDS) with autologous stem cell transplantation (ASCT) vs intensified chemotherapy megaCEOP in high risk diffuse large cell lymphoma (DLCL): no difference in outcome and toxicity. The Italian Lymphoma Intergroup, Italy. Blood 2001;98:725a[abstract].
17. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993;329:987-94.
18. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of reporting of meta-analyses. Lancet 1999;354:1896-900.
19. Cortelazzo S, Rossi A, Bellavita P, Oldani E, Viero P, Buelli M, et al. Clinical outcome after autologous transplantation in non-Hodgkin's lymphoma patients with high international prognostic index (IPI). Ann Oncol 1999;10:427-32.
20. Fanin R, Sperotto A, Ruiz De Elvira C, Zaja F, Stocchi R, Geromin A, et al. A retrospective analysis of 144 patients with aggressive non-Hodgkin's lymphoma: impact of autologous stem cell transplantation in first remission on outcome. Haematologica 2000;85:943-51.
21. Pettengell R, Radford JA, Morgenstern GR, Scarffe JH, Harris M, Woll PJ, et al. Survival benefit from high-dose therapy with autologous blood progenitor-cell transplantation in poor-prognosis non-Hodgkin's lymphoma. J Clin Oncol 1996;14:586-92.
22. Glass B, Kloess M, Engert A, Berdel WE, Metzner B, Trümper LH, et al. Mega-CHOEP repeated high dose therapy as treatment of aggressive NHL: critical impact of time scheduling. Blood 2002;100:776a[abstract].

Pre-publication Report & Outcomes of Peer Review

Contributions

We gratefully thank Prof. N. J. Milpied, Nantes, for providing detailed information on data so far only available in abstract form. We thank Prof. Dr. K.G. Blume, Stanford (USA), Prof. N. Schmitz, Hamburg, and Prof. T. Sauerbruch, Bonn (Germany), for critically reviewing the manuscript, and Mrs. U. Moser and Mr. S. Gütgemann for excellent secretarial help.

Disclosures

Conflict of interest: none

Redundant publications: parts of this manuscript were orally presented at the 44th annual meeting of the American Society of Hematology in Philadelphia, PA, USA, on December 9, 2002 [Blood 2002;100:(11) 181a].

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received August 18, 2003; accepted October 6, 2003.

In the following paragraphs, Professor Cazzola summarizes the peer-review process and its outcomes.

What is already known on this topic

High-dose chemotherapy (HDT) followed by autologous bone marrow transplantation (ABMT) has been extensively employed in the treatment of patients with aggressive non-Hodgkin's lymphomas. However, the role of therapeutic approach is still controversial since randomized trials comparing HDT/ASCT with conventional therapy have generated conflicting results.

What this study adds

This meta-analysis shows very heterogeneous results within prospective, randomized clinical trials with HDT/ASCT as a first-line therapy of aggressive non-Hodgkin's lymphomas. Based on this, HDT/ASCT cannot be recommended as standard first line treatment for patients with aggressive non-Hodgkin's lymphomas.