Conventional chemotherapy (CHOEP-14) with rituximab or high-dose chemotherapy (MegaCHOEP) with rituximab for young, high-risk patients with aggressive B-cell lymphoma: an open-label, randomised, phase 3 trial (DSHNHL 2002-1)

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Summary

Background High-dose therapy (HDT) followed by transplantation of autologous haemopoietic stem cells is frequently done as part of first-line therapy in young patients with high-risk aggressive B-cell lymphoma. We investigated whether HDT with cytotoxic agents identical to those used for conventional therapy followed by autologous stem-cell transplantation (ASCT) improved survival outcome compared with conventional chemotherapy when rituximab was added to both modalities.

Methods We did an open-label, randomised trial comparing conventional chemotherapy (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone) and rituximab (R-CHOEP-14) with dose-escalated sequential HDT and rituximab (R-MegaCHOEP) followed by repetitive ASCT in high-risk (age-adjusted International Prognostic Index [IPI] 2 or 3) patients aged 18–60 years with aggressive B-cell lymphoma. Eligible patients received radiotherapy for bulky, extranodal disease, or both. Randomisation (1:1) used the Pocock minimisation algorithm; patients were stratified by age-adjusted IPI factors, bulky disease, and centre. The primary endpoint was event-free survival. All analyses were done on the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT00129090.

Findings 136 patients were randomly assigned to R-CHOEP-14 and 139 to R-MegaCHOEP. 130 patients in the R-CHOEP-14 group and 132 in the R-MegaCHOEP group were included in the intention-to-treat population. After a median of 42 months (IQR 29–59), 3-year event-free survival was 69·5% (95% CI 61·3–77·7) in the R-CHOEP-14 group and 61·4% (52·8–70·0) in the R-MegaCHOEP group (p=0·14; hazard ratio 1·3, 95% CI 0·9–2·0). All 128 evaluable patients treated with R-MegaCHOEP had grade 4 leucopenia, as did 48 (58·5%) of 82 patients with documented blood counts in the R-CHOEP-14 group. All 128 evaluable patients in the R-MegaCHOEP group had grade 3–4 thrombocytopenia, as did 26 (33·8%) of 77 patients in the R-CHOEP-14 group with documented blood counts. The most important non-haematological grade 3 or 4 adverse event was infection, which occurred in 96 (75·0%) of 128 patients treated with R-MegaCHOEP and in 40 (31·3%) of 128 patients treated with R-CHOEP-14.

Interpretation In young patients with high-risk aggressive B-cell lymphoma, R-MegaCHOEP was not superior to conventional R-CHOEP therapy and was associated with significantly more toxic effects. R-CHOEP-14 with or without radiotherapy remains a treatment option for these patients, with encouraging efficacy.

Funding Deutsche Krebshilfe.

Published **Online** November 16, 2012 http://dx.doi.org/10.1016/S1470-2045(12)70481-3

See **Online/Comment** http://dx.doi.org/10.1016/S1470-2045(12)70507-7

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Introduction

Diffuse large B-cell lymphoma is the most common subtype of clinically aggressive lymphomas and comprises about a third of all B-cell lymphomas. With modern treatment strategies survival varies between about 50% and more than 90%,[1] largely dependent on clinical risk factors first described by the International Prognostic Index (IPI).[2] For young patients aged 18 to 60 years with high-risk disease many investigators worldwide use high-dose therapy (HDT) followed by transplantation of autologous blood-derived haemopoietic stem cells (ASCT) as part of first-line therapy.[3–11] Rituximab, a monoclonal anti-CD20 antibody, has substantially improved treatment outcomes for both old and young low-risk patients with diffuse large B-cell lymphoma.[12,13] No published study specifically looked into the efficacy of adding rituximab to standard CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CHOP-like chemotherapy, or HDT/ASCT in young, high-risk patients with aggressive B-cell lymphoma. To assess the efficacy of high-dose chemotherapy necessitating transplantation of autologous haemopoietic stem cells, the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) initiated the 2002-1 trial, which compared aggressive conventional chemotherapy (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone [CHOEP-14]) with HDT comprising multiple cycles of identical, but dose-escalated cytotoxic agents

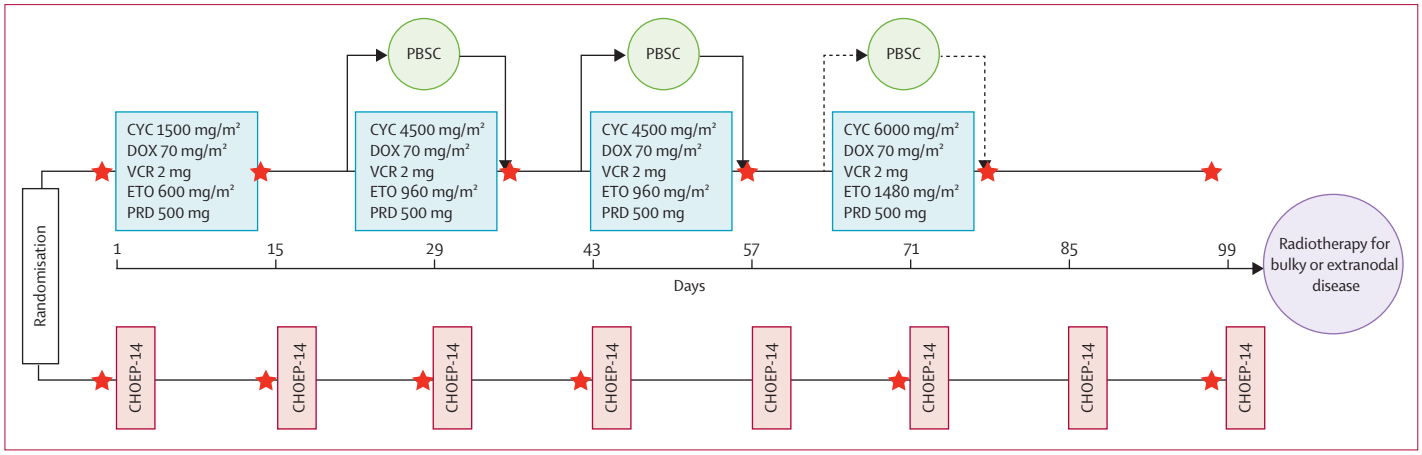

Figure 1: **Study design**
Doses of the drugs administered with the MegaCHOEP programme (CHOEP with escalated the doses of cyclophosphamide, etoposide, and doxorubicin) varied with each treatment cycle as indicated. Vincristine and prednisone are absolute doses. Doses for cyclophosphamide, doxorubicin, and etoposide are reported as mg/m². Stars represent one infusion of rituximab. CYC=Cyclophosphamide. DOX=doxorubicin. ETO=etoposide. PRD=prednisone. VCR=vincristine. CHOEP-14=cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone. PBSC=peripheral blood stem cells.

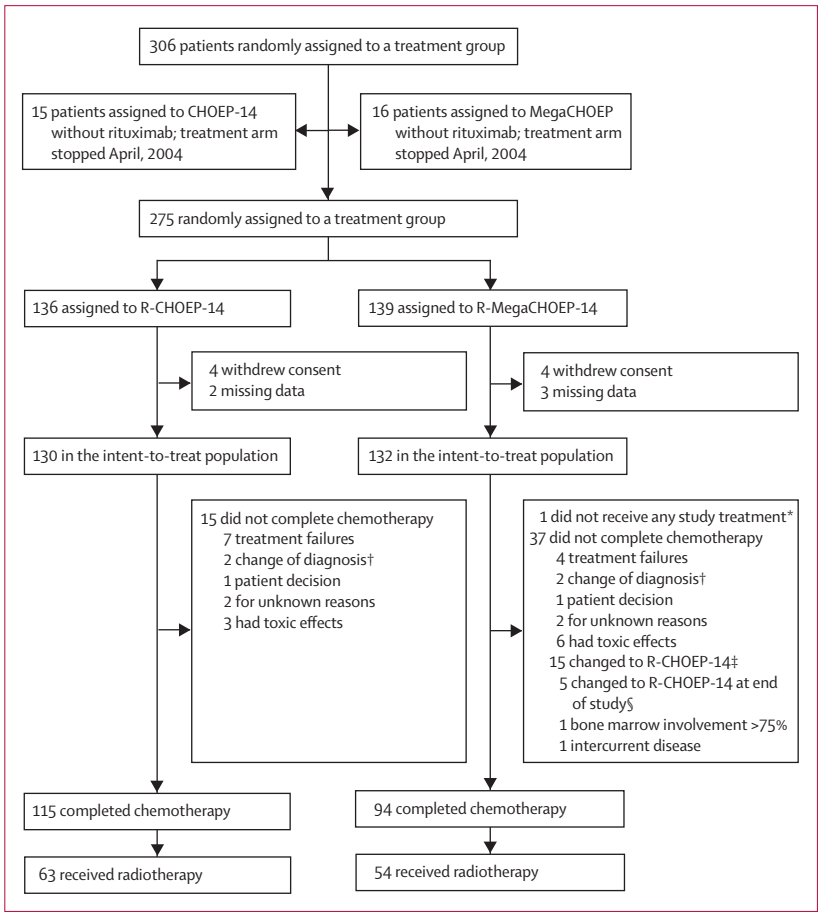

Figure 2: **Trial profile**
The doses of the drugs administered with the MegaCHOEP regimen (CHOEP with escalated doses of cyclophosphamide, etoposide, and doxorubicin) varied with each treatment cycle as shown in figure 1. R-CHOEP-14=cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone, and rituximab. R-MegaCHOEP=R-CHOEP with escalated doses of cyclophosphamide, etoposide, and doxorubicin. *Due to CNS disease detected after randomisation. †Due to incoming reference pathology. ‡The protocol stipulated for a change of treatment arm in case of mobilisation failure or excessive toxic effects. §As recommended by the data safety and monitoring committee.

(MegaCHOEP) and combined both regimens with rituximab (R-CHOEP-14 and R-MegaCHOEP). The trial was designed as a proof-of-principle study to address the role of dose-intensity in the rituximab era.

Methods

Patients

Between March 3, 2003, and April 7, 2009, we did a prospective, randomised, open-label, phase 3 study at 61 centres experienced in lymphoma treatment including ASCT. Eligible patients were between 18 years and 60 years of age who presented with biopsy-proven, untreated, CD20-positive, aggressive B-cell lymphoma.[14] The diagnosis was reviewed by a panel of six reference pathologists. Only patients with two or three risk factors (Ann Arbor stage III or IV, elevated lactate dehydrogenase, Eastern Cooperative Oncology Group [ECOG] performance status 2 or 3) of the age-adjusted IPI were eligible.[2] Patients with diagnosis of any malignancy other than aggressive B-cell lymphoma, substantial impairment of cardiac, pulmonary, hepatic, or renal function, bone-marrow infiltration more than 25%, active hepatitis, known HIV-positivity, or hypersensitivity to any study drug, or simultaneous participation in other clinical studies were excluded. No lymphoma-directed therapy except for prednisone (100 mg orally for 3 days) and vincristine (2 mg) was allowed before study entry.

Our study complied with the declaration of Helsinki and respected the guidelines of good clinical practice. The institutional review board or ethics committee of each participating centre approved the study protocol and its amendment. All patients gave written informed consent.

Randomisation and masking

The trial was not masked. After obtaining informed consent investigators faxed the registration form to the

study office in Hamburg, Germany, where inclusion and exclusion criteria were checked. Randomisation was done in a 1:1 ratio with the Pocock minimisation algorithm[15] at the Institute for Medical Informatics, Statistics, and Epidemiology in Leipzig, Germany. Treatment allocation was stratified by age-adjusted IPI factors, presence of bulky disease, and centre. The study started as a four-arm study with two arms identical to the ones described below but without rituximab. The study group met in April 17, 2004, and decided to stop enrolment into arms without rituximab. Since June 3, 2004, the study continued as outlined below.

Procedures

Patients had baseline assessments including history, clinical status, laboratory tests, CT scans of neck, chest, and abdomen, and a bone-marrow biopsy. Further investigations were done when indicated. Tumour measurements were done by the treating physician or the local radiologist. Performance status was defined according to the ECOG scale,[16] lactate dehydrogenase levels were expressed as the ratio of observed over the upper normal value. The stage of disease was defined according to the Ann Arbor classification. Figure 1 shows the study design. Conventional chemotherapy consisted of eight cycles of CHOEP at 2-week intervals (CHOEP-14) supported by granulocyte colony-stimulating factor. Each cycle comprised 750 mg/m² of cyclophosphamide, 50 mg/m² of doxorubicin, 2 mg of vincristine administered on day 1, 100 mg/m² of etoposide on days 1–3, and 100 mg of prednisone on days 1–5. The MegaCHOEP regimen used identical cytotoxic agents but escalated the doses of cyclophosphamide, etoposide, and doxorubicin.[17] The dose of doxorubicin was increased to 70 mg/m² in all four cycles. The doses of cyclophosphamide and etoposide were escalated to 1500 mg/m² and 600 mg/m² in cycle 1, 4500 mg/m² and 960 mg/m² in cycles 2 and 3, and 6000 mg/m² and 1480 mg/m² in cycle 4. To allow for continuation of treatment every 3 weeks blood-derived haemopoietic stem cells were harvested after treatment cycles 1, 2, and (optionally) 3. Granulocyte colony-stimulating factor (2×5 µg/kg per day) was started on day 6 after cycle 1 and continued until a minimum of 2×10⁶ CD34-positive progenitor cells per kg bodyweight had been collected for reinfusion after cycle 2. The mobilisation procedure was repeated after cycle 2 and the collection product was split into two each of which needed to contain more than 2×10⁶ CD34-positive cells per kg bodyweight to be transplanted after cycle 3 and cycle 4. If the yield of the second collection was insufficient, another harvest was done after cycle 3. Patients with failure to mobilise stem cells or who had excessive toxic effects on R-MegaCHOEP were requested to continue therapy with R-CHOEP-14 until eight cycles had been administered.

Rituximab (375 mg/m²) was administered on day 0 of cycles 1–4, 6, and 8 of the R-CHOEP-14 and on days 0, 14, 36, 56, 77, and 98 of the R-MegaCHOEP regimen.

	R-CHOEP-14 (n=130)	R-MegaCHOEP (n=132)
Sex		
Male	82 (63·1%)	82 (62·1%)
Female	48 (36·9%)	50 (37·9%)
Age, years	50 (18–60)	47 (19–60)
Lactate dehydrogenase level		
Elevated more than normal	127 (97·7%)	128 (97·0%)
Ann Arbor stage		
III or IV	126 (96·9%)	127 (96·2%)
ECOG performance status		
0–1	88 (67·7%)	88 (66·7%)
>1	42 (32·3%)	44 (33·3%)
Number of extranodal sites		
0–1	74 (56·9%)	75 (56·8%)
>1	56 (43·1%)	57 (43·2%)
B-symptoms*		
Yes	71 (55·0%)	81 (61·8%)
No	58 (45·0%)	50 (38·2%)
Bulky disease		
Yes	77 (59·2%)	81 (61·4%)
No	53 (40·8%)	51 (38·6%)
Bone marrow involvement		
Yes	16 (12·3%)	10 (7·6%)
No	114 (87·7%)	122 (92·4%)
Age-adjusted International Prognostic Index		
2	95 (73·1%)	97 (73·5%)
3	35 (26·9%)	35 (26·5%)
Histology		
Not reviewed	8 (6·2%)	3 (2·3%)
Reviewed	122 (93·8%)	129 (97·7%)
DLBCL	101 (82·8%)	101 (78·3%)
Follicular lymphoma (grade III)	4 (3·3%)	6 (4·7%)
Follicular lymphoma and DLBCL	3 (2·5%)	3 (2·3%)
Burkitt's lymphoma	1 (0·8%)	..
Burkitt-like lymphoma	1 (0·8%)	1 (0·8%)
Blastic mantle-cell lymphoma	1 (0·8%)	1 (0·8%)
Aggressive marginal-zone lymphoma	2 (1·6%)	1 (0·8%)
Unclassified B-cell lymphoma	7 (5·7%)	10 (7·8%)
No aggressive B-cell lymphoma	1 (0·8%)	4 (3·1%)
Technically insufficient material	1 (0·8%)	2 (1·6%)

Data are n (%) or media (range). R-CHOEP-14=cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone, and rituximab. R-MegaCHOEP=R-CHOEP with escalated doses of cyclophosphamide, etoposide, and doxorubicin. ECOG=Eastern Cooperative Oncology Group. DLBCL=Diffuse large B-cell lymphoma. *One missing value per arm.

Table 1: **Baseline characteristics**

Thus, doses and dose intensities of rituximab were identical and timing was very similar in both treatment arms (figure 1). Radiotherapy (36 Gy, administered at daily doses of 1·8 to 2 Gy over 4 weeks) was mandatory for all patients with bulky disease defined as any mass of 7·5 cm or larger at the largest diameter or extranodal involvement. Patients with meningeosis cerebri received

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See **Online** for appendix

	Cyclophosphamide (mg/m²)		Doxorubicin (mg/m²)		Vincristine (mg)		Etoposide (mg/m²)		Prednisone (mg)	
	MegaCHOEP	CHOEP	MegaCHOEP	CHOEP	MegaCHOEP	CHOEP	MegaCHOEP	CHOEP	MegaCHOEP	CHOEP
Planned dose	16 500	6000	280	400	8	16	4000	2400	2000	4000
Dose received*	98%	98%	99%	99%	100%	100%	96%	98%	100%	100%
Planned dose per week	1375	375	23·3	25	0·7	1	333·3	150	166·7	250
Dose received*	85%	92%	87%	92%	88%	85%	82%	91%	91%	93%

*Median % of planned dose or dose intensity.

Table 2: **Dose and dose intensities**

	R-CHOEP-14 (n=127)	R-MegaCHOEP (n=126)
Complete and unconfirmed response	100 (78·7%)	90 (71·4%)
Complete and unconfirmed response and additional treatment	1 (0·8%)	2 (1·6%)
Partial response	2 (1·6%)	5 (4·0%)
No change	2 (1·6%)	2 (1·6%)
Progressive disease	13 (10·2%)	15 (11·9%)
Therapy-associated death	4 (3·1%)	7 (5·6%)
Unknown	5 (3·9%)	5 (4·0%)

Data are n (%). Response to treatment was assessed in accordance with the International Workshop 1999 Critera.[18] R-CHOEP-14=cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone, and rituximab. R-MegaCHOEP=R-CHOEP with escalated doses of cyclophosphamide, etoposide, and doxorubicin.

Table 3: **Response to treatment by treatment group**

15 mg of methotrexate, 40 mg of cytosine arabinoside, and 4 mg of dexamethasone intrathecally on days 1 and days 5 of each treatment cycle with leucovorin rescue until no lymphoma cells could be detected in cerebrospinal fluid. CNS prophylaxis was mandatory for any patient with involvement of bone marrow, testes, or the skull region and consisted of 15 mg of methotrexate intrathecally on days 1 and 5 of cycles 1 and 2.

Tumour response was assessed 2 months after end of therapy in both treatment arms. Responses were classified as complete remission, unconfirmed complete remission, partial remission, stable disease, and progressive disease using international workshop criteria.[18] Follow-up visits were scheduled every 3 months for the first 2 years after end of therapy, every 6 months for years 3 to 5, and annually thereafter.

All adverse events defined as any adverse change from baseline characteristics were retrieved in predefined categories from case report forms. Each event was graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0).[19]

Statistical analysis

The trial was initially planned in a 2×2 factorial design to compare patients randomly assigned to receive eight cycles of CHOEP-14 with those assigned to the MegaCHOEP regimen. We originally wanted to also compare patients randomly assigned to rituximab or no rituximab. However, on June 3, 2004, the study arms without rituximab were closed. A 15% difference between R-CHOEP-14 and R-MegaCHOEP was regarded as clinically relevant to justify the additional toxic effects and effort of HDT. Therefore, we aimed to identify a difference of 15% in 3-year event-free survival (hazard ratio 0·563) with a two-sided significance level of 5% and a power of 80%, requiring 328 patients for the intention-to-treat analysis. To achieve full power for the planned per-protocol analysis, 368 patients needed to be included (software for sample size calculations: nQuery Advisor 2.0). The first planned interim analysis was done after 185 patients had been enrolled and showed that the stopping rule according to O'Brien and Fleming[20] used to show the superiority of R-MegaCHOEP over R-CHOEP was not fulfilled. We also did conditional power calculations to test whether the study aim could still be achieved. The probability to show superiority of R-MegaCHOEP over R-CHOEP-14 at the end of trial was only 6·2%. Following a decision of the data monitoring and safety committee, the trial was stopped in April 7, 2009, with 306 patients randomly assigned. Because the steering committee recommended switching patients on treatment with R-MegaCHOEP to R-CHOEP-14, response assessment was restricted to 127 patients treated with R-CHOEP-14 and 126 patients treated with R-MegaCHOEP. For Kaplan-Meier analyses patients on treatment were censored on the date of change.

Primary analyses were done by intention-to-treat. Event-free survival, progression-free survival, and overall survival were measured from the date of randomisation, estimated according to Kaplan-Meier, and differences between groups were compared by the log-rank test. The primary endpoint was event-free survival (defined as time from randomisation to disease progression, start of salvage treatment, additional, unplanned treatment, relapse, or death from any cause). Secondary endpoints were response, progression during treatment, frequency of toxic effects, progression-free survival (defined as time from randomisation to progression, relapse, or death from any cause; patients with complete response or unconfirmed complete response and additional treatment were censored) and overall survival (defined as time from randomisation to death from any cause). Kaplan-

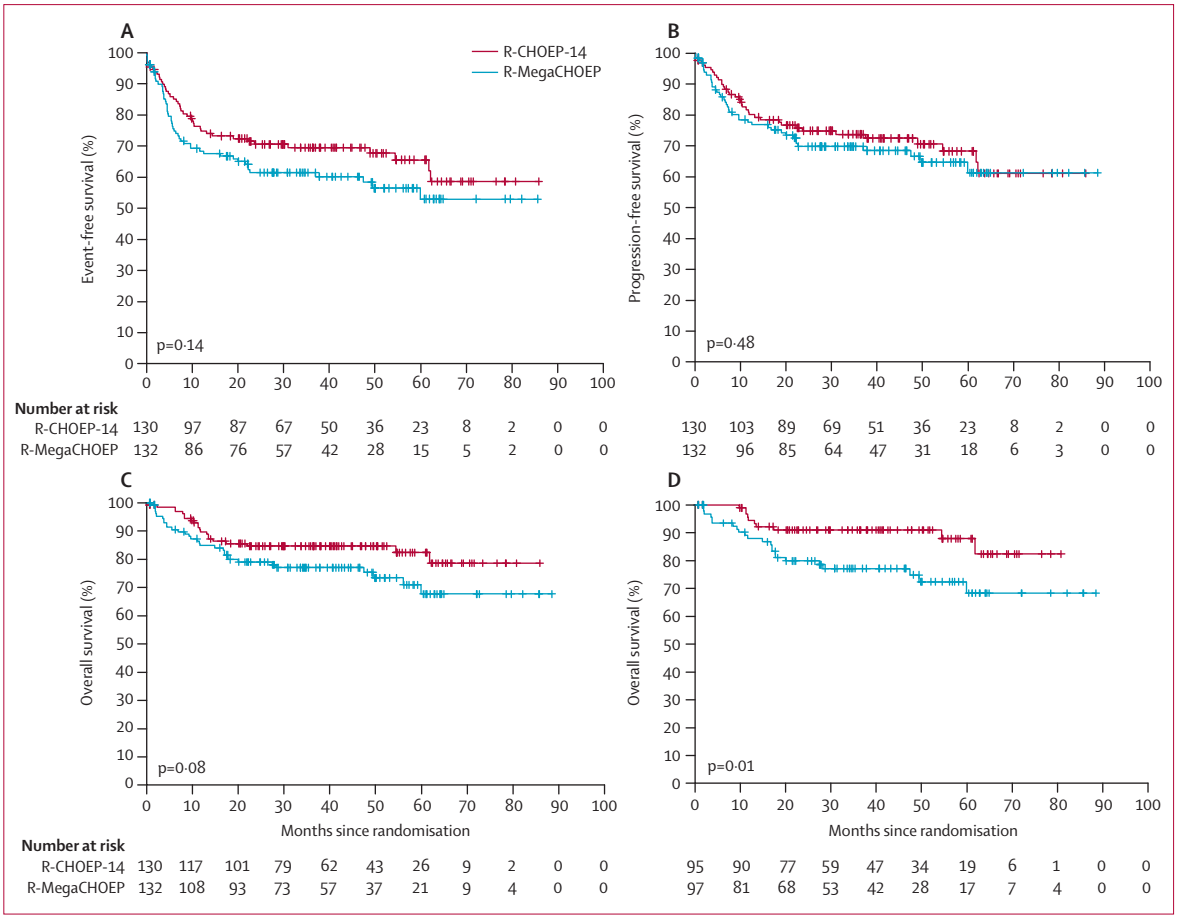

Figure 3: **Kaplan-Meier estimates of outcomes by treatment group in the intention-to-treat population**
Event-free survival (A), progression-free survival (B), and overall survival (C) for the intention-to-treat population. Overall survival for the 192 patients with age-adjusted IPI 2 (D). R-CHOEP-14=cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone, and rituximab. R-MegaCHOEP=R-CHOEP with escalated doses of cyclophosphamide, etoposide, and doxorubicin.

Meier estimates at 3 years, with 95% CIs, were calculated for event-free survival, progression-free survival, and overall survival. Multivariable analyses were done with Cox proportional-hazard models adjusted for stratification variables. Sensitivity analyses (ie, per-protocol analyses, complete treatment analyses) were done to assess the robustness of the results. Subgroup analyses according to the age-adjusted IPI were done as planned in the study protocol to investigate whether the treatment effects were homogeneous. Baseline characteristics were reported as percentages except for age, which was reported as the median. Qualitative data (eg, non-haematological toxic effects) were analysed by use of χ^2 test and, if necessary, by Fisher's exact test. Relative dose and relative dose-intensity were assessed according to the Kaplan-Meier method as described elsewhere.[21] Differences between groups were classed as significant for p values less than or equal to 0·05. Statistical analyses of efficacy were done with SPSS PASW 18. This study is registered with ClinicalTrials.gov, number NCT00129090.

Role of the funding source
Staff members of the DSHNHL were responsible for distribution and collection of case report forms, data entry, and validation, coordination of monitoring procedures, elaboration of queries, adverse event reporting, statistical analyses, and production of the study report. Annual study group meetings served as platforms for progress reports and decisions on trial conduct. Deutsche Krebshilfe, who provided funding for study, had no role in study design, data collection and analysis, interpretation or writing the report. All authors had full access to the raw data in this study and the corresponding author had final responsibility for the decision to submit for publication.

Results
We enrolled 306 patients, 31 of whom were treated without rituximab (figure 2). 262 patients with CD20-positive, aggressive B-cell lymphoma received chemotherapy and rituximab and formed the intention-to-treat-population of this analysis. More than 90% of those patients received prephase therapy with vincristine and prednisone.

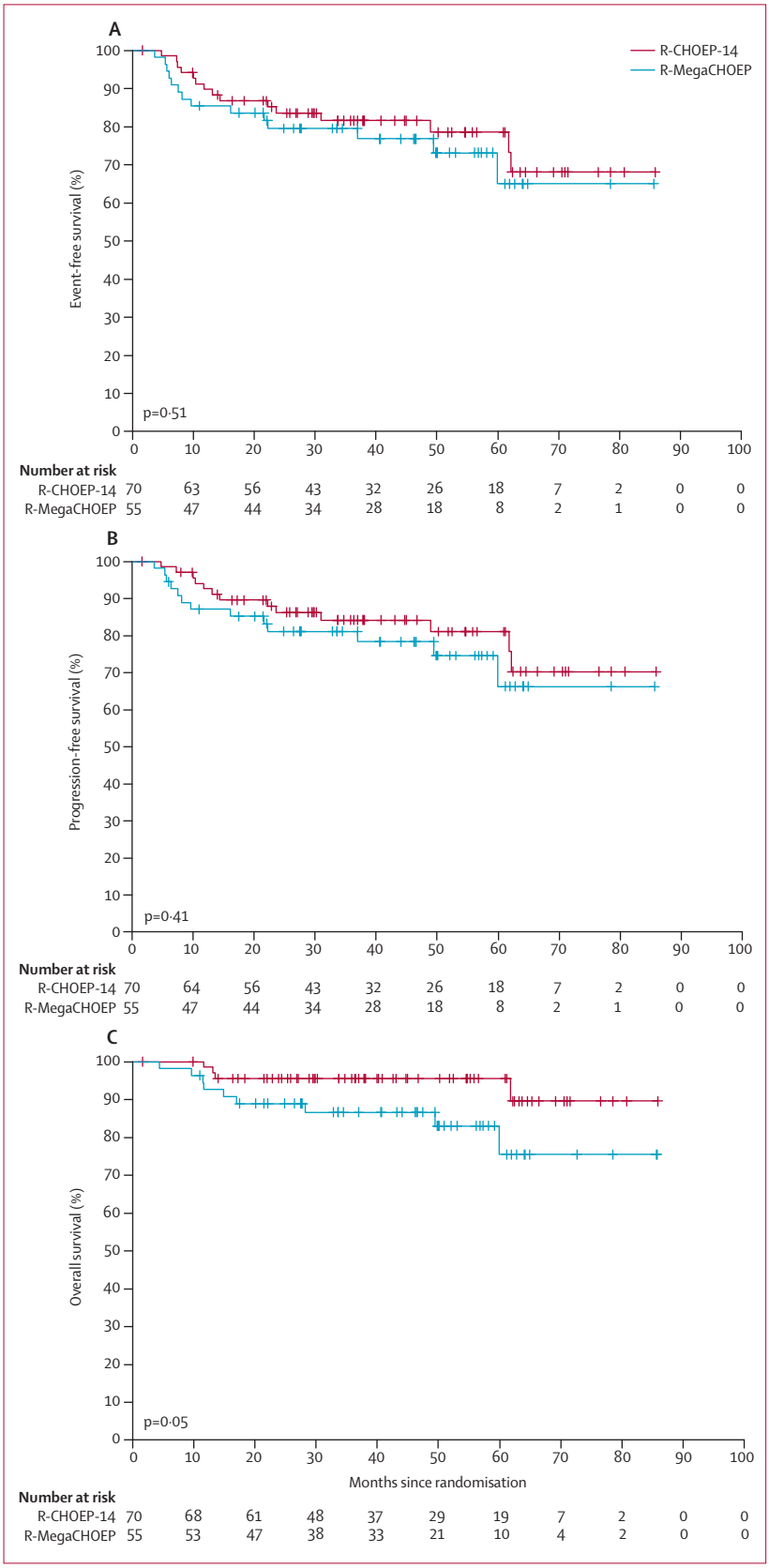

Figure 4: **Kaplan-Meier estimates of outcomes by treatment group in patients who received all treatment as per protocol**
Event-free survival (A), progression-free survival (B), and overall survival (C). R-CHOEP-14=cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone, and rituximab. R-MegaCHOEP=R-CHOEP with escalated doses of cyclophosphamide, etoposide, and doxorubicin.

Patient characteristics did not differ significantly between arms (table 1). Close to 80% of patients in both treatment arms had diffuse large B-cell lymphoma; the other subtypes of aggressive B-cell lymphoma are specified in table 1. Most patients scored an age-adjusted IPI of 2; age-adjusted IPI was 3 in about 27% of patients, mainly reflecting their poor performance status.

15 patients (11·5%) did not complete R-CHOEP-14 and 38 (28·8%) did not complete R-MegaCHOEP for reasons detailed in the trial profile (figure 2). Besides lymphoma progression, changes of diagnosis, and individual patient decisions, three patients in the conventional arm and 21 patients in the experimental arm did not complete therapy as randomised because of toxic effects. Six of these 21 patients stopped study treatment while 15 patients continued therapy with R-CHOEP-14 as stipulated in the protocol. At the end of study, five patients on treatment with R-MegaCHOEP were switched to R-CHOEP-14 because of ethical concerns expressed by the data monitoring and safety committee and study group members.

The planned administered doses and dose intensities for all drugs are compared in table 2. According to protocol, 63 (48·5%) of 130 patients treated with R-CHOEP-14 and 54 (40·9%) of 132 patients treated with R-MegaCHOEP were irradiated for bulky or extranodal disease. There was no significant difference in the proportion of patients who achieved a complete or unconfirmed response (p=0·18) or an overall response (p=0·35; table 3).

After a median of 42 months (IQR 29–59), 3-year event-free survival was estimated at 69·5% (95% CI 61·3–77·7) for patients treated with R-CHOEP-14 and 61·4% (52·8–70·0) for patients treated with R-MegaCHOEP (p=0·14; hazard ratio 1·3, 95% CI 0·9–2·0). 3-year progression-free survival was 73·7% (95% CI 65·9–81·5) after treatment with R-CHOEP-14 and 69·8% (61·6–78·0) after treatment with R-MegaCHOEP (p=0·48). 3-year overall survival was 84·6% (95% CI 78·3–90·9) for patients treated with R-CHOEP-14 compared with 77·0% (69·6–84·4) for patients treated with R-MegaCHOEP (p=0·08; figure 3). Patients with age-adjusted IPI 2 had significantly better event-free survival if treated with R-CHOEP-14 (75·5% [95% CI 66·5–84·5] in the R-CHOEP-14 group *vs* 63·5% [53·5–73·5] in the R-MegaCHOEP group; p=0·0509) and overall survival (91·0% [95% CI 85·1–96·9] *vs* 77·1% [68·3–85·9]; p=0·01; figure 3) while no significant differences were seen if patients with age-adjusted IPI 3 only were assessed (event-free survival: 53·9% [95% CI 37·2–70·6] *vs* 55·5% [38·6–72·4];

p=0·92; overall survival: 68·1% [95% CI 52·6–83·6] *vs* 76·5% [62·2–90·8]; p=0·75). Because a sizeable fraction of patients randomly assigned to R-MegaCHOEP were unable to complete treatment we did a further analysis restricting the comparison of R-CHOEP-14 and R-MegaCHOEP to 125 patients who had received all treatment per protocol. No significant differences were seen in event-free survival (p=0·51), progression-free survival (p=0·41), or overall survival (p=0·051) between treatment arms (figure 4). In multivariate analyses of event-free survival and overall survival adjusted for strata no other factors significantly influencing treatment outcome were found (data not shown). Figure 5 shows the event-free survival of 293 patients treated on study including the 31 patients who did not receive rituximab before these treatment arms were closed.

A median of $6·5\times10^6$ CD34-positive blood cells were transplanted after cycle 2 of R-MegaCHOEP, $4·6\times10^6$ after cycle 3, and $4·2\times10^6$ after cycle 4. Neutrophil (absolute neutrophil count $>0·5\times10^9$ per L) and platelet (platelets $>50\times10^9$ per L) recovery occurred after a median of 13 days and 14 days after cycle 1, 15 days and 16 days after cycle 2, 15 days and 18 days after cycle 3, and 16 days and 20 days after cycle 4; no graft failures were reported. All evaluable patients (n=128) in the R-MegaCHOEP group had WHO grade 4 leucopenia; granulocyte colony-stimulating factor was used in 95·3% of all treatment cycles and in 128 of 129 patients (99·2%) on R-CHOEP-14, but 48 (58·5%) of 82 patients with documented blood counts still developed grade 4 leucopenia. All evaluable patients in the R-MegaCHOEP group had grade 3–4 thrombocytopenia; 26 (33·8 %) of 77 patients on R-CHOEP-14 with documented blood counts had grade 3 or 4 thrombocytopenia. Platelet transfusions were needed in 115 (91·3%) of 128 patients in the R-MegaCHOEP group and 13 (10·5%) of 124 patients in the R-CHOEP-14 group with documented platelet counts. Anaemia was frequent and necessitated the transfusion of red blood cells in 117 (92·9%) of 126 in the R-MegaCHOEP arm and 80 (63·5%) of 126 patients in the R-CHOEP-14 arm. Patients on R-MegaCHOEP developed more mucositis, diarrhoea, nausea, and vomiting, which together with the substantial neutropenia contributed to the 75·0% incidence of severe infections in these patients (table 4). Sensory neurological side-effects were more common after R-CHOEP-14, which might be due to the higher cumulative dose of vincristine administered (p=0·02). Overall, 32 patients on R-MegaCHOEP and 21 patients on R-CHOEP-14 died; causes of death are listed in table 5. R-MegaCHOEP not only caused more deaths related to toxic effects than did R-CHOEP-14 (5·6% *vs* 3·1%) but also more patients died from lymphoma (16 patients as opposed to nine patients after R-CHOEP-14). Nine secondary malignancies have occurred to date (3·6%) with no significant differences between treatment arms: four patients were diagnosed with myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML), or solid tumours (n=2) after R-CHOEP-14, five patients were diagnosed with MDS, AML, and epidermoid cancer or solid tumours (n=3) after R-MegaCHOEP.

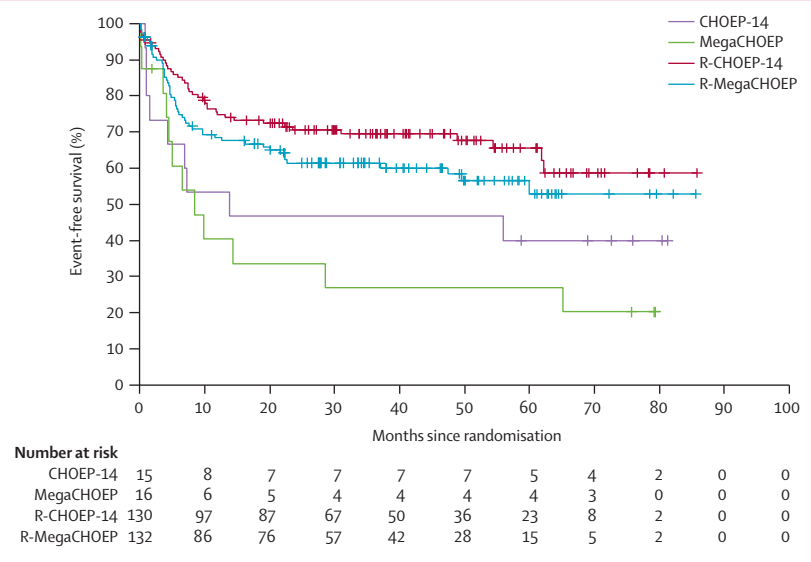

Figure 5: **Kaplan-Meier estimates of event-free survival for patients who received R-CHOEP-14 or R-MegaCHOEP with or without rituximab**
CHOEP-14=cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone. MegaCHOEP=CHOEP-14 with escalated doses of cyclophosphamide, etoposide, and doxorubicin. R-CHOEP-14=cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone, and rituximab. R-MegaCHOEP=R-CHOEP with escalated doses of cyclophosphamide, etoposide, and doxorubicin.

	R-CHOEP-14 (n=130)	R-MegaCHOEP (n=132)
Infection	40/128 (31·3%)	96/128 (75·0%)
Mucositis	10/121 (8·3%)	81/125 (64·8%)
Nausea	1/120 (0·8%)	21/123 (17·1%)
Diarrhoea	4/120 (3·3%)	14/122 (11·5%)
Vomiting	2/119 (1·7%)	13/123 (10·6%)
Psychiatric disorders	2/119 (1·7%)	7/122 (5·7%)
Arrhythmia	0	5/122 (4·1%)
Sensory	10/124 (8·1%)	2/121 (1·7%)

Data are number (%) of patients with a documented event during ≥1 treatment cycle. R-CHOEP-14=cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone, and rituximab. R-MegaCHOEP=R-CHOEP with escalated doses of cyclophosphamide, etoposide, and doxorubicin.

Table 4: **Grade 3–4 non-haematological adverse events by treatment arm**

Discussion

In young patients aged 18 to 60 years with high-risk (age-adjusted IPI 2 or 3) aggressive B-cell lymphoma R-CHOEP-14 administered every 2 weeks was associated with high remission rates. Our results for event-free, progression-free, and overall survival after R-CHOEP-14 in such patients are the most encouraging to date (panel). However, R-MegaCHOEP was no better than

	R-CHOEP-14	R-MegaCHOEP
Number of deaths (%)*	21/127 (16·5%)	32/126 (25·4%)
Tumour related	9	16
Therapy-related (only study treatment)	4	7
Therapy-related (including salvage)	10	10
Secondary neoplasia	2	3
Concomitant disease	1	3
Other or unknown	..	2

R-CHOEP-14=cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone, and rituximab. R-MegaCHOEP=R-CHOEP with escalated doses of cyclophosphamide, etoposide, and doxorubicin. *In some cases more than one cause of death was documented.

Table 5: **Cause of death**

***Panel:* Research in context**

Systematic review

We searched Medline from January, 2002, to June, 2012, with search terms "aggressive B-cell lymphoma" or " diffuse large B-cell lymphoma" and "rituximab" and "young patients" or "patients younger than 60" for reports published in English and German. We identified one trial comparing chemoimmunotherapy (R-CHOEP) with chemotherapy alone[13] and one trial comparing two chemoimmunotherapy regimens.[22] Neither trial assessed young, high-risk patients with age-adjusted International Prognostic Index (IPI) 2 or 3. We did not identify any trial comparing conventional therapy with high-dose therapy both combined with rituximab.[23–25] These latter studies compared conventional chemotherapy (R-CHOP or R-CHOP-like[23–25]) to classic high-dose therapy (BEAM [BCNU, etoposide, cytosinearabinoside, melphalan] or total-body-irradiation-based) in combination with rituximab.

Interpretation

Our study shows that aggressive conventional chemoimmunotherapy (R-CHOEP-14) gives excellent results in young, high-risk patients with aggressive B-cell lymphoma, which cannot be improved with high-dose therapy necessitating autologous stem cell transplantation. This finding is strengthened by the fact that we used identical cytotoxic drugs for both conventional and high-dose therapy.

R-CHOEP-14 in terms of efficacy, and was associated with significantly more toxicity, suggesting that in the rituximab era HDT followed by ASCT does not improve outcome for this group of patients.

In the pre-rituximab era, survival of young, high-risk patients with diffuse large B-cell lymphoma varied from 55% to 67%[3–11] after conventional chemotherapy whereas full reports in randomised trials with rituximab-containing regimens have not been published yet. Recent abstracts with short follow-up showed 2-year progression-free survival of 63% and overall survival of 75% after (R)-CHOP-21,[23] event-free survival of 56% and overall survival of 83% after R-CHOP-14 for patients with age adjusted IPI 2–3,[24] and progression-free survival of 59% and overall survival of 83% after R-CHOP-14 or R-Mega-CHOP.[25] While survival rates after CHOP-21 or R-CHOP-21 were not separately reported by Stiff and colleagues,[23] the event-free survival after R-CHOP-14 for patients with age adjusted IPI 2 or 3 in Le Gouill and colleagues' study[24] was 13·5 % lower, progression-free survival after R-MegaCHOP[25] was 14·5% lower than reported here for R-CHOEP-14.

We speculate that the higher event-free survival and progression-free survival reported for R-CHOEP-14 reflects the integration of etoposide into the CHOP regimen. The addition of etoposide to CHOP was pioneered by Koeppler and colleagues[26] more than 25 years ago and since that time CHOEP has continuously been used to treat high-risk patients with aggressive B-cell and T-cell lymphoma in Germany.[27] A prospective, randomised study from the pre-rituximab era adopted this strategy and confirmed the superiority of CHOEP over CHOP in young patients with normal lactate dehydrogenase levels.[28] Although a randomised comparison of R-CHOP to R-CHOEP has not been done, the study group members of the DSHNHL had voted in favour of R-CHOEP-14 and against R-CHOP-14 when the design of the current study was previously discussed in 2000–01. In addition to the results of the randomised study by Pfreundschuh and colleagues[28] the major reasons for this decision were two-fold: first, we wanted to make sure that a potentially superior survival of patients treated with HDT/ASCT could not be explained by the poor results obtained with conventional chemotherapy. This strategy had been successfully implemented when we compared HDT/ASCT to an aggressive conventional salvage chemotherapy in patients with relapsed Hodgkin's disease.[29] Second, and most importantly, the study group members expressed strong ethical concerns that CHOP chemotherapy would show unsatisfactory activity in young, high-risk patients. For this reason, the precursor of the current DSHNHL study from the prerituximab era had already used CHOEP instead of CHOP in the conventional treatment arm.[8] R-CHOEP has also been used in other countries, for instance, an early report from Sweden[30] and a population-based analysis from Denmark[31] support that etoposide significantly adds to the efficacy of R-CHOP-14. Finally, the Groupe d'Etude des Lymphomes de l'Adulte (GELA) recently reported superior results in young patients with age-adjusted IPI 1 comparing their R-ACVBP (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) regimen to R-CHOP-14.[22] Like the CHOEP regimen, ACVBP uses higher doses of cyclophosphamide and doxorubicin and adds additional cytotoxic agents (vindesine and bleomycin). Radiotherapy for bulky and extranodal disease might also have contributed to the favourable outcome of our patients.[32]

In the studies mentioned above, patients were randomly assigned to either conventional or high-dose therapy. While the study done in the USA lacked the statistical power to compare the results of R-CHOP-21 with R-CHOP-21 followed by HDT/ASCT,[23] the study done in France came to the same conclusion as our study.[24] In patients who were PET-negative after four courses of R-CHOP-14, HDT/ASCT did not improve progression-free survival or overall survival as compared with four more courses of R-CHOP-14.

Another study in Italy reported a significantly better progression-free survival for chemosensitive patients who proceeded to transplantation; overall survival was not significantly different.[25] However, neither 2-year progression-free survival (63%) nor overall survival (80%) after HDT/ASCT were better than the 2-year progression-free survival (75%) and overall (85%) after R-CHOEP-14. We therefore suggest adding a standard dose of etoposide to CHOP and giving local radiotherapy rather than exposing patients to the higher risks and discomfort of HDT/ASCT. We did not address the point that classic HDT with BEAM (BCNU, etoposide, cytosin-arabinoside, melphalan) followed by ASCT might improve progression-free survival in patients who respond to a limited number of conventional chemotherapy courses with the R-CHOP regimen, and therefore cannot rule it out.

While all other studies used established high-dose regimens (BEAM or total-body-irradiation-based), we chose to use identical drugs in both the conventional and the high-dose regimen to address the proof-of-principle question of whether dose escalation of cytotoxic agents improves outcome also in the rituximab era. HDT was administered to all patients who could possibly receive it and was not restricted to patients achieving complete remission or partial remission with conventional chemotherapy. Extensive phase 2 studies with[33] and without[34] rituximab have shown that the time interval between cycles of MegaCHOEP could not be further shortened and six cycles were not superior to four cycles.[17] Current analyses show that even patients able to receive the full R-MegaCHOEP programme did not have better outcomes than after R-CHOEP-14.

We conclude that further escalation of dose or dose-intensity within a high-dose regimen is not possible and would not be effective. Because of the high efficacy of R-CHOEP we stopped using HDT/ASCT as part of first-line therapy in high-risk (age-adjusted IPI 2, 3) patients with aggressive B-cell lymphoma. In these young patients, R-CHOEP-14 was no more toxic than R-CHOP, was feasible in an outpatient basis, and was highly effective. R-CHOEP-14, therefore, represents a valid alternative to other regimens. Further improvement is certainly necessary, especially in patients with age-adjusted IPI 3. Ongoing investigations will show if those patients not responding to rituximab and combination chemotherapy belong to biological high-risk groups characterised by gene-expression profiling[35] or the presence of *MYC* and *BCL2* translocations.[36] We recently showed that variations in rituximab dosing can improve event-free survival and overall survival in elderly high-risk patients with diffuse large B-cell lymphoma.[37] Therefore, we are investigating if doubling the number of rituximab infusions from six to 12 will also improve outcome of younger patients.

Contributors

NS, MZ, ML, and BG designed the study. NS, MN, MZ, MH, PB, CS, AV, MB, NP, GE, GD, LT, MP, and BG recruited patients and obtained study data. AR was responsible for histological review. CR designed radiotherapy and was responsible for radiological review. MZ and ML did the biometric analyses. NS, MN, MZ, ML, and BG analysed and interpreted the data and wrote the report. All authors reviewed and approved the final report.

Conflicts of interest

NS and MP were members of Roche advisory boards. BG, NS, MP, and AR have received research support from Roche. All other authors declare that they have no conflicts of interest.

Acknowledgments

This work was supported by the Deutsche Krebshilfe (70-2732-pf4). We thank Ulrike Schoenwiese, Beate Mann (Institute for Medical Informatics, Statistics, and EpidemiologyLeipzig), and Corinna Endler (Asklepios Hospital St Georg Hamburg) for data management, Martina Kunert and Barbara Wicklein for data base development (IMISE Leipzig), and Huei-Shan Wu (Asklepios Hospital St Georg Hamburg) for secretarial assistance.

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