original article

Dose-escalated CHOEP for the treatment of young patients with aggressive non-Hodgkin's lymphoma: II. Results of the randomized high-CHOEP trial of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL)

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On behalf of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL)

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Background: The addition of etoposide to combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone [etoposide to combination chemotherapy with cyclophosphamide, vincristine and prednisone (CHOEP)] improved outcome of young patients with good-prognosis aggressive lymphoma. To improve results further, the maximal dose-escalated version of CHOEP-21 tolerable without stem-cell support (high CHOEP: cyclophosphamide 1400 mg/m^2, doxorubicin 65 mg/m^2, vincristine 2 mg, etoposide 175 mg/m^2 ×3, prednisone 100 mg ×5) was compared with CHOEP-21.
Patients and methods: Intention-to-treat analysis of 389 young (18–60 years) patients with good-prognosis (age-adjusted International Prognostic Index = 0, 1) aggressive lymphoma randomized to CHOEP-21 (*n* = 194) or high CHOEP (*n* = 195).
Results: There was no difference in 3-year event-free (64% versus 67%; *P* = 0.734) or overall survival (83% versus 87%; *P* = 0.849). Neither low-risk nor low-intermediate risk patients benefited from high CHOEP. High CHOEP was more toxic than CHOEP-21 (grades 3 and 4 leukocytopenia 100% versus 87.2%, *P* < 0.001; thrombocytopenia 80.8% versus 9.6%, *P* < 0.001; infections 35% versus 11%, *P* < 0.001; therapy-associated deaths 3.1% versus 0%, *P* = 0.03).
Conclusion: Dose-escalated CHOEP-21 does not provide clinical benefit for young patients with good-prognosis aggressive lymphomas. Since differences between chemotherapy regimens are compressed by the addition of rituximab, the results of this trial have bearing on strategies aiming to improve outcome of good-prognosis aggressive lymphomas in the rituximab era.
Key words: aggressive NHL, chemotherapy models, clinical trials, dose escalation

introduction

The Deutsche Studiengruppe für Hochmaligne Non-Hodgkin-Lymphome (DSHNHL) showed that the addition of etoposide to combination chemotherapy with cyclophosphamide,

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doxorubicin, vincristine and prednisone (CHOP)[etoposide to combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOEP)] improves outcome of young patients with good-prognosis aggressive lymphoma [1] and is associated with less central nervous system (CNS) relapses [2]. The superiority of CHOP over CHOEP in these patients was confirmed by the MabThera International Trial Group (MInT) study [3]. In a randomized study with two- and three-weekly CHOEP, where leukocytopenia (<1 × 10^9/l) lasting longer than 4 days or

a thrombocytopenia ($<20 \times 10^9$/l) had been defined as dose limiting, only a moderate dose escalation was feasible with CHOEP-14 (cyclophosphamide 1200 mg/m^2, doxorubicin 60 mg/m^2, etoposide 400 mg/m^2), while a higher dose escalation was achieved with the three-weekly CHOEP-21 (cyclophosphamide 1600 mg/m^2, doxorubicin 70 mg/m^2, etoposide 600 mg/m^2) [4]. According to the 'effective dose' concept [5], this dose level of CHOEP-21 was predicted to confer a higher effective dose than the maximal tolerated dose level achieved with the biweekly regimen and should improve long-term event-free survival (EFS) by 8%–10%. Therefore, and because of the higher total dose achievable with the three-weekly regimen, the three-weekly regimen at one dose level below the maximal tolerated dose (the 'maximal practicable dose' in a nationwide study) was designated 'high CHOEP' and was chosen for comparison with baseline CHOEP-21 in this randomized trial.

patients and methods

patients

The study was conducted in accordance with the Helsinki declaration. The protocol was approved by the ethics committee of each participating center. All patients gave written informed consent. Eligible were patients 18–60 years old with untreated aggressive lymphoma according to the World Health Organization classification [6] with none or one risk factor according to the age-adjusted International Prognostic Index (aaIPI) [7] with an Eastern Cooperative Oncology Group (ECOG) performance status of zero to three. Exclusion criteria included transformed or secondary lymphoma, primary CNS or gastrointestinal mucosa-associated lymphoid tissue lymphoma, significant dysfunction of major organs, known human immunodeficiency virus or active chronic hepatitis B or C infection. Histological diagnosis was reviewed by a panel of five expert hematopathologists and was available in >99% of the cases.

staging

The stage of lymphoma was defined by means of physical examination, relevant laboratory parameters [complete blood cell count and blood chemistry including lactate dehydrogenase (LDH)], computed tomography of the chest, abdomen, bone marrow biopsy and other investigational procedures depending on clinical symptoms. All patients had measurements of their maximal tumor mass. Bulky disease was defined as the presence of a tumor mass with a maximal diameter ≥7.5 cm.

treatment

Patients were randomly assigned to receive CHOEP-21 or high CHOEP-21 (Table 1) with stratification for center, bulky disease and aaIPI factors (LDH, stage and ECOG). Granulocyte colony-stimulating factor (G-CSF) (filgrastim or lenograstim) was mandatory for patients receiving high CHOEP-21 and was at the physician's discretion for patients receiving CHOEP-21. Patients were to receive radiotherapy (36 Gy) to sites of primary bulky and extranodal disease.

end points and assessment of response

The primary end point was EFS; secondary end points were response, progression under therapy, progression-free survival, overall survival (OS) and frequency of toxic effects. EFS was defined as time from randomization to progressive disease under therapy, no achievement of complete remission (CR) or no achievement of unconfirmed complete remission (CRu), partial remission; no change, relapse after CR or CRu, additional therapy or death from any cause.

Table 1. Dosages of the CHOEP-21 and high-CHOEP-21 regimens

	CHOEP-21	High CHOEP-21
Cyclophosphamide	750 mg/m^2, i.v. day 1	1400 mg/m^2, i.v. day 1
Doxorubicin	50 mg/m^2, i.v. day 1	32.5 mg/m^2, i.v. days 1 and 2
Etoposide	100 mg/m^2, i.v. days 1–3	175 mg/m^2, i.v. days 1–3
Vincristine	2 mg, i.v. day 1	2 mg/m^2, i.v. day 1
Predniso(olo)ne	100 mg, p.o. days 1–5	100 mg, p.o. days 1–5

CHOEP, etoposide to combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone.

CR and CRu were defined according to the International Workshop criteria [8]. CR and CRu lasting <2 months were counted as progression. Progression under therapy was defined as the proportion of patients with progressive disease during treatment and within 2 months after the end of treatment. Progression-free survival was defined as time from randomization to progression under therapy, progression after partial remission, no change, relapse or death from any cause; additional treatment was censored for this end point. OS was defined as time from randomization to death from any cause.

Response was assessed according to the International Workshop criteria [8] after the end of therapy by physical examination, relevant laboratory parameters, computed tomography of the chest and abdomen, bone marrow biopsy for previous involvement by lymphoma and the control of all other previous pathological findings by adequate investigational procedures. Follow-up evaluation was carried out every 3 months in the first 2 years after treatment and every 6 months from third up to the fifth year after treatment.

statistical analysis

We aimed to identify a difference of 10% in the 3-year EFS rate with a two-sided significance level of 5% and a power of 80%, requiring 670 patients. Main analyses were done by intention-to-treat. Rates of response, progression under therapy and therapy-associated deaths were analyzed by using χ^2 test, and if required by Fisher's exact tests. EFS, progression-free survival, OS and time to relapse after achieving CR or CRu and without any therapy were measured from the date of randomization and estimated according to Kaplan–Meier [9]. Multivariate analyses were done by using Cox proportional hazard models [10] to estimate hazard ratios for having an event. Sensitivity analyses (i.e. per protocol analyses) of the primary and secondary end points were done to assess the robustness of the results. Differences between groups were regarded as significant for P values <0.05 (two sided). Toxic effects were graded according to National Cancer Institute—Common Toxicity Criteria. For the estimation of treatment duration, dose intensity and dose erosion, the technique of Kaplan–Meier estimators were used. Patient characteristics, therapeutic interventions and CTC toxic effects were compared by using χ^2 test, and if required by Fisher's exact tests. Statistical analyses were carried out with SPSS (version 11.5) and StatXact (version 5). This trial was registered as DSHNHL-1999-2 with the registration numbers EU-20242 and NCT00053768.

results

From 1 July 2000 to 4 December 2003, 392 patients were enrolled at 122 participating institutions (see Appendix). Enrolment was stopped on 5 December 2003 upon recommendation of the DSHNHL protocol review committee

because superiority of CHOP-like regimens plus rituximab over CHOP-like regimens alone in young patients with good-prognosis diffuse large B-cell lymphoma (DLBCL) had been demonstrated in the MInT study [3]. Three patients were excluded because of missing or revoked informed consent, leaving 194 patients allocated to CHOEP-21 and 195 patients allocated to high CHOEP-21 assessable on an intention-to-treat basis. The demography of the study (Table 2) shows the typical characteristics of a young population with good-prognosis

Table 2. Characteristics of patients

	CHOEP-21 (n = 194)	Hi-CHOEP (n = 195)
Age (years), median (range)	45 (18–60)	48 (20–60)
Sex: male, no. (%)	114 (59)	103 (53)
Histology		
With central review, no. (%)	194 (100)	195 (100)
Without central review, no. (%)	1 (<1)	–
B cell	153 (79)	157 (81)
DLBCL total	114 (59)	129 (66)
DLBCL, NOS	37 (19)	33 (17)
DLBCL, centroblastic	53 (27)	71 (36)
DLBCL, immunoblastic	2 (1)	5 (3)
DLBCL, plasmoblastic	2 (1)	1 (<1)
DLBCL, T-cell rich B cell	5 (3)	4 (2)
DLBCL, anaplastic large cell		3 (<2)
DLBCL, mediastinal B-cell lymphoma	15 (8)	12 (6)
Follicular lymphoma III	12 (6)	13 (7)
Follicular lymphoma III plus DLBCL	15 (8)	6 (3)
Burkitt lymphoma	2 (1)	0 (0)
Mantle cell lymphoma (blastoid)	1 (<1)	0 (0)
Aggressive marginal zone lymphoma	1 (<1)	2 (1)
Burkitt like	1 (<1)	1 (<1)
NOS	3 (<2)	5 (3)
Unclassified (technically insufficient)	4 (2)	1 (<1)
T cell	32 (17)	29 (15)
Anaplastic large cell	22 (11)	17 (9)
ALK positive	9 (5)	6 (3)
ALK negative	5 (3)	9 (5)
Large anaplastic T cell, NOS	8 (4)	2 (1)
Other peripheral T-cell lymphomas	10 (5)	12 (6)
Composite lymphoma	1 (<1)	1 (<1)
Indolent lymphoma	5 (3)	2 (1)
Hodgkin lymphoma		3 (<2)
No aggressive lymphoma		2 (1)
Unclassified (technically insufficient)	2 (1)	1 (<1)
Bulky disease (≥7.5 cm) at randomization, no. (%)	65 (34)	61 (31)
Stage III/IV, no. (%)	46 (24)	49 (25)
Lactate dehydrogenase level elevated, no. (%)	38 (20)	40 (21)
Age-adjusted IPI, no. (%)		
0	108 (56)	104 (53)
1	84 (43)	89 (46)
2	2 (1)	2 (1)

CHOEP, etoposide to combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone; DLBCL, diffuse large B-cell lymphoma; NOS, not otherwise specified; ALK, anaplastic lymphoma kinase; IPI, International Prognostic Index.

aggressive lymphoma, with the two cohorts being well balanced for clinical and histological characteristics. In all, 54.5% of the patients had none, 44.5% one and 1% had two risk factors according to the aaIPI. Central pathology review was done in all cases except one (insufficient material).

treatment

The median duration of treatment from day one of the first cycle until the last day of chemotherapy in cycle 6 was 109 days for CHOEP-21 and 111 days for high CHOEP. Dose reductions for the myelosuppressive drugs cyclophosphamide, doxorubicin and etoposide were only allowed if the criteria for hematopoietic recovery (defined as leukocytes $>2.5 \times 10^9$/l, platelets $>75 \times 10^9$/l) had not been reached >7 days after the scheduled start of the next chemotherapy cycle. As shown in the cumulative dose plots (Figure 1), the median relative doses and median relative dose intensities for cyclophosphamide were 99%, and 96%, respectively, in the CHOEP-21 arm, while the relative dose of cyclophosphamide in the high-CHOEP-21 group was 93%, and the relative dose intensity of cyclophosphamide was 90%. This resulted in a clear difference of the actual received doses of cyclophosphamide between the two groups. The relative doses and relative dose intensities for doxorubicin were 99% and 96% after CHOEP-21 and 95% and 91% after high CHOEP-21, respectively; for etoposide, the figures were 100% (relative dose) and 96% (relative dose intensity) in CHOEP-21 and 93% (relative dose) and 90% (relative dose intensity) in high CHOEP-21. In all, 98% of the patients treated with high CHOEP and 34% of the patients with CHOEP-21 received G-CSF for a median of 7 days after each chemotherapy cycle. All patients completed treatment, except for patients where treatment was stopped early because of toxicity (CHOEP-21: $n = 1$; high CHOEP: $n = 10$; $P = 0.006$) or nonresponse (CHOEP-21: $n = 9$; high CHOEP: $n = 2$; $P = 0.032$).

The percentages of patients who received radiotherapy according to protocol were similar between the groups (CHOEP-21: 85%; high CHOEP: 89%). Two patients after CHOEP-21 and three after high CHOEP received additional (i.e. unplanned) radiotherapy, while seven patients after CHOEP-21 and six after high CHOEP did not receive the planned radiotherapy to bulky disease.

outcome

After CHOEP-21, 152 of 194 [78.4%; 95% confidence interval (CI) 72% to 84%] and after high CHOEP, 155 of 195 (79.5%; 95% CI 73% to 85%) patients achieved CR or CRu. This difference was not significant ($P = 0.783$). Twenty-four patients (12.4%; 95% CI 8.1% to 17.9%) progressed under CHOEP-21 and 19 (9.7%; 95% CI 6.0% to 14.8%) under high CHOEP; again, this difference was not significant ($P = 0.409$).

After 37 months of median observation (range 0.03–61.0 months), there was no difference in the primary end point EFS between CHOEP-21 (3-year EFS rate: 64%; 95% CI 56% to 71%) and high CHOEP (3-year EFS rate: 67%; 95% CI 60% to 74%; $P = 0.734$). The 3-year progression-free survival was also not different (CHOEP-21: 70% 95% CI 63% to 77%; high CHOEP: 74%; 95% CI 67% to 80%; $P = 0.856$).

We registered 60 deaths: 30 after CHOEP-21 (28 lymphoma associated, one due to concomitant disease, one unknown) and 30 after high CHOEP (21 lymphoma associated, six treatment related, one each due to concomitant disease and secondary neoplasm and one unknown). Three-year OS was 83% (95% CI 77% to 89%) for patients allocated to CHOEP-21 and 87% (95 CI 82% to 92%; $P = 0.849$) for patients allocated to high CHOEP (Figure 2).

In multivariate analyses for EFS, the occurrence of events was affected by elevated pretreatment serum LDH [relative risk (RR) = 2.2; 95% CI 1.5–3.4; $P < 0.001$] and advanced stage III/IV (RR = 2.1; 95% CI 1.4–3.1; $P < 0.001$), but not by treatment arm (RR = 0.9; 95% CI 0.7–1.3; $P = 0.711$) or by ECOG performance status of one or more (RR = 0.9; 95% CI 0.2–3.5; $P = 0.842$). The lack of prognostic impact of a performance status of one or more is explained by the low number of patients with this presentation (1% in each treatment arm). Similarly, with respect to OS, only elevated LDH (RR = 2.4; 95% CI 1.3–4.5; $P = 0.005$) and advanced stage (RR = 2.3; 95% CI 1.3–4.1; $P = 0.005$) had prognostic impact, but not treatment arm.

sensitivity analyses

Sensitivity (i.e. per protocol) analyses of patients who met the eligibility criteria of aggressive lymphoma confirmed by histopathological review, and who met all eligibility criteria and did not have a major protocol violation, confirmed the results of the intention-to-treat analyses with regard to all end points. Moreover, results remained unchanged if only the patients with DLBCL (CHOEP-21: 144; high CHOEP: 129) were analyzed.

A subgroup analysis of patients with no or one risk factor according to the aaIPI (Figure 3) showed that neither subgroup benefited from dose-escalated high CHOEP (aaIPI = 0: 3-year EFS 75%, 95% CI 66% to 83% versus 75%, 95% CI 66% to 84%, $P = 0.921$; aaIPI = 0: 3-year OS 91%, 95% CI 85% to 97% versus 93%, 95% CI 88% to 98%, $P = 0.568$; aaIPI = 1: 3-year EFS 49%, 95% CI 37% to 61% versus 59%, 95% CI 49% to 69%, $P = 0.599$; aaIPI = 1: 3-year OS 72%, 95% CI 61% to 83% versus 81%, 95% CI 73% to 89%, $P = 0.374$).

safety and toxicity

High CHOEP was associated with considerably more grades 3 and 4 leukocytopenia, thrombocytopenia, anemia, infections
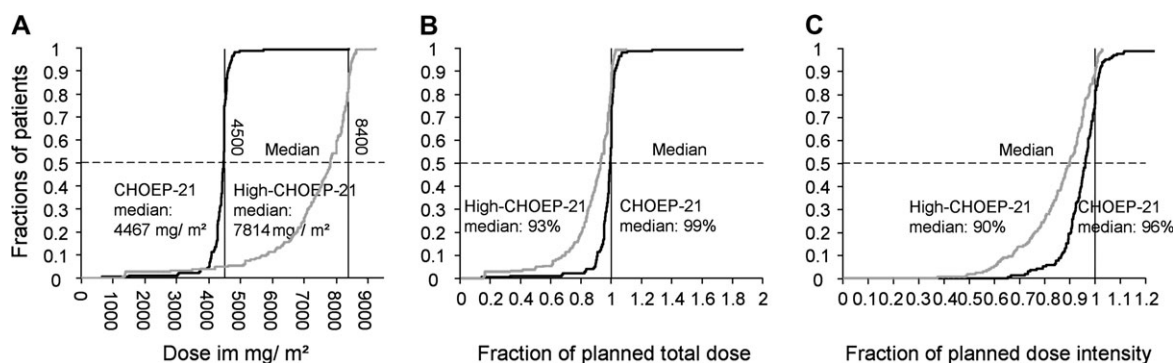

Figure 1. Absolute doses, cumulative dose plots of relative doses and relative dose intensities of cyclophosphamide after etoposide to combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOEP)-21 and high CHOEP-21. The differences in the median planned total doses of cyclophosphamide (4500 mg/m^2 in the CHOEP-21 and 8400 mg/m^2 in the high-CHOEP-21 arm) were largely maintained in the actual multicenter trial (4467 mg/m^2 in the CHOEP-21 and 7814 mg/m^2 in the high-CHOEP-21 arm) (A). The relative doses of cyclophosphamide were 99% after CHOEP-21 and 93% after high CHOEP-21 (B). The relative dose intensities were 96% and 90%, respectively (C).
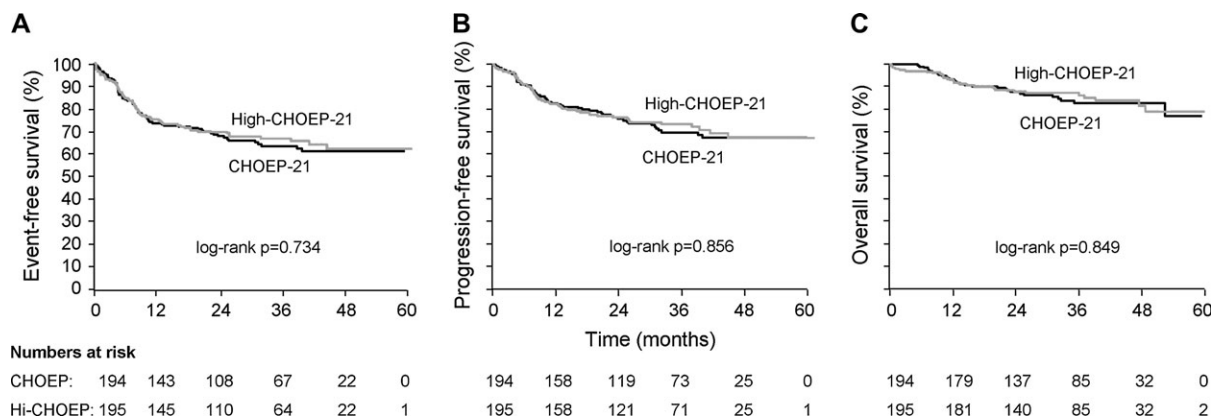

Figure 2. Event-free survival (A), progression-free survival (B) and overall survival (C) of young patients with good-prognosis aggressive lymphoma after etoposide to combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOEP)-21 and high CHOEP-21. No significant differences were observed.
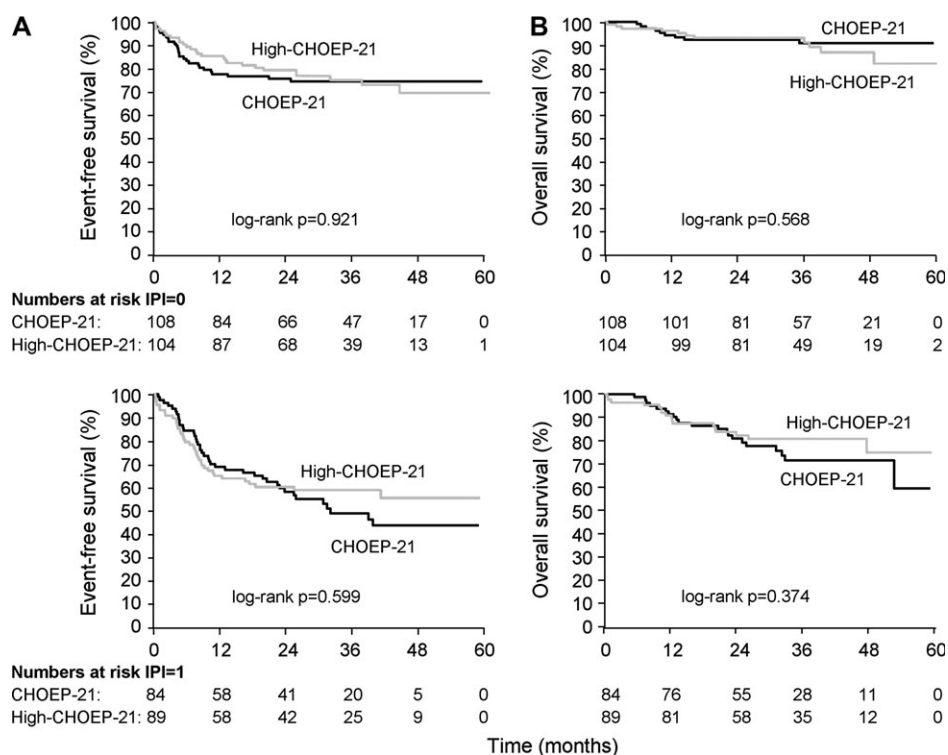
Figure 3. Event-free survival (A) and overall survival (B) of young patients with good-prognosis aggressive lymphoma after etoposide to combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOEP)-21 and high CHOEP-21. Neither the low-risk [no age-adjusted International Prognostic Index (aaIPI) risk factor; upper row] nor the low-intermediate risk group patients (one aaIPI risk factor; lower row) profits from the dose-escalated high-CHOEP-21 regimen.

and mucositis, necessitating more red blood cell and platelet infusions and i.v. antibiotics (Table 3).

There were eight secondary neoplasms: four after CHOEP-21 (two prostate cancers, one panniculitis-like T-cell lymphoma and one breast cancer) and four after high CHOEP (one myelodysplastic syndrome, one acute myelogenous leukemia, one mycosis fungoides and one acute lymphoid leukemia).

discussion

Both the NHL-B1 trial of the DSHNHL [1] and the MInT [3] study had shown significant superiority of CHOEP over CHOP in young good-prognosis patients with aggressive lymphoma. Moreover, in contrast to other dose intensifications of CHOP [11], no increase in secondary myelodysplastic syndromes and acute myeloid leukemias was observed after CHOEP. Since the baseline CHOEP-21 was well tolerated by young patients, further dose escalation seemed possible. To define this more precisely, we carried out a randomized dose-escalation study [4] which showed that higher dose escalation was possible in a three-weekly than in a two-weekly modification of the CHOEP regimen. Because the effective dose model [5], which had successfully predicted the improvement of dose-intensified regimens in Hodgkin's disease [12], indicated a significant improvement of the dose-escalated high CHOEP-21 over baseline CHOEP, we hoped to identify a difference of 10% in the 3-year EFS rate with a two-sided significance level of 5% and a power of 80%, requiring 670 patients. When the first

Table 3. Side-effects and therapeutic interventions

	CHOEP-21 (%)	Hi-CHOEP (%)	
Toxicity			
Leukocytopenia	87.2	100	$P < 0.001$
Thrombocytopenia	9.6	80.8	$P < 0.001$
Anemia	11.8	54.1	$P < 0.001$
Infection	10.8	34.6	$P < 0.001$
Polyneuropathy	3.3	3.8	$P = 0.793$
Mucositis	2.7	8.1	$P = 0.022$
Cardiac toxicity	0.5	1.6	$P = 0.317$
Renal toxicity	0.0	0.5	$P = 0.318$
Lung toxicity	0.0	0.5	$P = 0.318$
Nausea or vomiting	4.8	5.3	$P = 0.814$
Alopecia	69.8	73.1	$P = 0.503$
Therapeutic interventions			
Red blood cell transfusions			
Per patient	11.2	64.6	$P < 0.001$
Per cycle	4.1	28.3	$P < 0.001$
Platelet transfusion			
Per patient	2.1	32.8	$P < 0.001$
Per cycle	0.4	12.4	$P < 0.001$
Antibiotics (i.v.)			
Per patient	32.6	63.5	$P < 0.001$
Per cycle	8.7	23.0	$P < 0.001$

CHOEP, etoposide to combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone.

interim analysis of the MInT trial [3], however, showed a significantly better outcome for young patients with good-prognosis DLBLC patients after the addition of the monoclonal CD20 antibody rituximab to six cycles of a CHOP-like regimen, the protocol review committee of the DSHNHL recommended to stop enrolment into the high-CHOEP study. Thus, instead of the planned 670 patients, only 389 were recruited and assessable.

The results of this trial show that the considerable dose escalation of the high-CHOEP-21 regimen did not improve the outcome of young good-prognosis patients, despite excellent adherence to the protocol with relative doses and relative dose intensities of the cytotoxic drugs >93% in all treatment arms securing significant differences between CHOEP-21 and high CHOEP with respect to the received total drugs and drug intensities. This indicates that the role of dose escalation in young good-prognosis patients with aggressive lymphoma is small and was overestimated by the effective dose concept [5]. In this respect, it is interesting that in a recent randomized trial of the Groupe d'Etude de Lymphomes de l'Adulte (GELA) [13], the ACVBP regimen, which can be regarded as both a dose-dense (biweekly) and a dose-escalated modification of the CHOP regimen, achieved excellent results in patients with low-risk (aaIPI = 0) aggressive lymphoma and compared favorably to three cycles of CHOP plus involved-field therapy [14], an approach which many investigators had considered standard for these patients. Similarly, a randomized comparison of classical CHOP-21 with dose-dense and intensified 'I-CHOP' (CHOP-14 with 1000 mg/m^2 cyclophosphamide and 70 mg/m^2 doxorubicin) showed an improved 6-year EFS and OS in young patients with low-intermediate (but not high-intermediate) risk after I-CHOP compared with standard CHOP-21 [15]. Also, a separate analysis of patients treated with CHOP-21, CHOP-14, CHOEP-21 and CHOEP-14 in the NHL-B1 trial showed that biweekly CHOEP-14 significantly improved CR rates, EFS and OS in young good-prognosis patients compared with CHOP-21, while CHOEP-21 did so only with respect to the primary end point EFS [1]. Finally, a recently published study in young patients with aggressive lymphoma compared eight cycles of CHOP with an intensified dose-dense approach [two cycles of a dose-dense modification of CHOP followed by a consolidation with high-dose methotrexate/cytarabine and stem-cell-supported BEAM (carmustine, etoposide, cytarabine and melphalane); all given within 64 days] and showed an advantage for the intensified approach compared with CHOP with respect to EFS for all patients included in that trial (12 aaIPI = 0, 80 aaIPI = 1, 105 aaIPI = 2) and with respect to survival for patients with aaIPI = 2 [16]. All these observations indicate that dose densification rather than dose escalation is the preferred strategy if improved outcome for young good-prognosis patients with aggressive lymphoma is the goal. Whether this also applies to poor-prognosis patients and/or to dose escalations necessitating stem-cell support cannot be answered by this study and must await the results of appropriately designed randomized trials which are currently carried out by the DHSNHL and several other study groups.

In the MInT study [3], both patients treated with CHOP-21 and CHOEP-21 had a significantly improved outcome after the addition of rituximab, the CHOEP-21 patients albeit to a smaller extent. Moreover, while confirming the superiority of CHOEP-21 over CHOP-21, the MInT study also showed that after the addition of rituximab, CHOP is as good as CHOEP and due to its lower toxicity and easier handling, CHOP is the preferred chemotherapy partner for rituximab in this population. Nevertheless, CHOEP might still be the preferred chemotherapy regimen for young patients with aggressive lymphomas where rituximab is not indicated (e.g. CD20-negative aggressive B-cell lymphomas and T-cell lymphomas) or not tolerated.

The experience of the high-CHOEP study provides useful information for the design of future DLBCL trials in the rituximab era. Since the addition of rituximab compresses differences between chemotherapy regimens (chemo-equalizing effect), superiority of dose-escalated CHO(E)P over baseline CHO(E)P should even be less likely when these regimens are combined with rituximab.

The MInT trial had revealed that in the era of combined rituximab and CHOP, two subgroups can be distinguished among the young patients with good-prognosis DLBCL, a very favorable subgroup (no bulky disease, no risk factor) and a less favorable subgroup (bulky disease and/or 1 aaIPI risk factor). After six cycles of CHOP plus rituximab (and without radiotherapy), the 3-year EFS was 97% and the OS 100% in the very favorable subgroup. Because these results can hardly be improved, six cycles of CHOP plus rituximab has become the standard treatment for these patients in many parts of the world, and the DSHNHL is currently comparing only four with six cycles of CHOP plus rituximab in a randomized noninferiority study for these patients. Excellent results have also been reported by the Southwest Oncology Group who combined three cycles of CHOP-21 with rituximab followed by involved-field radiotherapy in a phase II trial [17], but more patients and longer follow-up of this study is needed to better define the role of this approach in good-prognosis patients.

In contrast to the favorable subgroup, the results obtained with six cycles of CHOP-21 plus rituximab in the less favorable (aaIPI = 1 and/or bulky disease) subgroup (3-year EFS rate 75%) definitely warrant further improvement. While high-dose regimens necessitating stem-cell support have not been tested in young good-prognosis patients, the results of the current high-CHOEP trial together with results from other trials using dose-dense regimens [15] and the subgroup analysis of the NHL-B1 trial indicate that dose-densified rather than dose-escalated modifications of the CHOP regimen hold promise for achieving the necessary improvement of outcome in young good-prognosis patients of the less favorable subgroup. This should be even more the case, as a considerable proportion of the young patients in the less favorable subgroup present with elevated LDH and/or bulky disease, two factors which have been shown to be particularly sensitive to a reduction of chemotherapy intervals [18]. Therefore, the DSHNHL recently started a multicenter trial which compares the MInT standard of six cycles of CHOP-21 plus rituximab with six cycles of dose-dense CHOP-14 plus rituximab for this population, and in a parallel study, the French GELA compares CHOP-21 plus rituximab with their dose-dense ACBVP regimen plus rituximab in young patients with one aaIPI risk factor.

funding

Appendix

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