original article

*Annals of Oncology* 19: 538–544, 2008
doi:10.1093/annonc/mdm497
Published online 22 January 2008

# Dose-escalated CHOEP for the treatment of young patients with aggressive non-Hodgkin's lymphoma: I. A randomized dose escalation and feasibility study with bi- and tri-weekly regimens

L. Trümper[1], C. Zwick[2†], M. Ziepert[3†], K. Hohloch[1], R. Schmits[2], M. Mohren[4], R. Liersch[5], M. Bentz[6], U. Graeven[7], U. Wruck[8], M. Hoffmann[9], B. Metzner[10], D. Hasenclever[3], M. Loeffler[3] and M. Pfreundschuh[2*]

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

*[1]Hematology and Oncology, University Hospital Göttingen; [2]Internal Medicine I, Saarland University Medical School, Homburg; [3]Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig; [4]Oncology, University Hospitals of Magdeburg, Magdeburg; [5]Oncology, University Hospital Münster, Münster; [6]Oncology, City Hospital of Karlsruhe, Karlsruhe; [7]Oncology, Kliniken Maria-Hilf, Mönchengladbach; [8]Helios-Kliniken, Bad Saarow; [9]Oncology, Städtische Kliniken Ludwigshafen, Ludwigshafen; [10]Department of Internal Medicine, Städtische Kliniken Oldenburg, Germany*

*Received 18 September 2007; accepted 21 September 2007*

**Background:** To determine the maximum tolerated dose of a bi- and tri-weekly combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone plus etoposide (CHOEP) regimen without stem-cell support.

**Patients and methods:** Randomized phase I/II multicenter four-level (cyclophosphamide: 1000–1200–1400–1600 mg/m$^2$; doxorubicin: 55–60–65–70 mg/m$^2$; etoposide: 375–450–525–600 mg/m$^2$) dose escalation study with CHOEP-14 and CHOEP-21 in young patients (18–60 years) with newly diagnosed aggressive non-Hodgkin's lymphoma. Dose-limiting toxicity was defined as thrombocytopenia <80 000/mm$^3$ and leukocytopenia <2500/mm$^3$ on days 16 (CHOEP-14) and 23 (CHOEP-21) or prolonged (>4 days) leukocytopenia (<1000/mm$^3$) or thrombocytopenia (<20 000/mm$^3$).

**Results:** One hundred and thirty-nine patients (high-CHOEP-14: 47, high-CHOEP-21: 92) were randomly allocated to the study. Maximal tolerated dose was level 2 for CHOEP-14 and level 4 for CHOEP-21. With a less favorable profile of patients in CHOEP-14, 4-year event-free survival was 47.9% after high-CHOEP-14 and 66.2% after high-CHOEP-21, 4-year overall survival 62.1% after high-CHOEP-14 and 73.4% after high-CHOEP-21, respectively.

**Conclusion:** Significant dose escalations of CHOEP are possible with granulocyte colony-stimulating factor support, with different chemotherapy models favoring the maximally escalated bi- or tri-weekly regimen, respectively. Because a higher total dose can be achieved with six cycles of the tri-weekly compared with the biweekly regimen, CHOEP-21 at dose escalation level 3 was chosen for a nationwide randomized comparison with baseline CHOEP-21 in a subsequent phase III trial.

**Key words:** aggressive NHL, chemotherapy models, clinical trials, dose escalation

## introduction

The addition of etoposide to combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOEP) improves outcome of young patients with good prognosis aggressive lymphoma [1]. The superiority of CHOEP over combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) in these patients was recently confirmed by the MabThera International Trial Group study [2], establishing CHOEP as the preferred regimen for young patients with aggressive lymphomas for whom rituximab is not indicated and/or cannot be given (e.g. CD20-negative cases or contraindications against rituximab). The low toxicity of CHOEP-21 and CHOEP-14 in young patients in the non-Hodgkin's lymphoma (NHL)-B1 trial [1] indicated that a dose escalation of the CHOEP regimen should be feasible both for the bi- and tri-weekly regimens. According to the dose-intensity concept [3] and the effective dose model [4], higher dose intensity and/or effective dose, respectively, were predicted to result in further improvement of the outcome with the CHOEP regimen. In order to determine the maximal dose of the CHOEP regimen tolerated

*Correspondence to:* Dr M. Pfreundschuh, Innere Medizin I, Saarland University Medical School, D-66421 Homburg, Germany. Tel: +49-6841-162-3002; Fax: +49-6841-162-3101; E-mail: inmpfr@uniklinikum-saarland.de

†Both authors contributed equally to this manuscript.

without stem-cell support, the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) initiated a randomized phase I/II dose escalation study for the CHOEP-14 and CHOEP-21 regimens, respectively, in untreated patients with aggressive NHL. Randomization was carried out to provide two unbiased independent estimates for the dose levels that can be achieved with either schedule but not to compare with outcomes.

## patients and methods

The study was conducted in accordance with the Helsinki Declaration. The protocol was approved by the ethics review 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 (WHO) classification [5] with a sufficient performance status [Eastern Cooperative Oncology Group (ECOG) scale 0–3]. In the original protocol, only patients with elevated lactate dehydrogenase (LDH) were eligible; after an amendment, patients with any risk profile according to the age-adjusted International Prognostic Index (IPI) [6] with the exception of patients in stage I without bulky disease were eligible. Excluded were patients with primary central nervous system or gastrointestinal mucosa-associated lymphoid tissue lymphoma, significant dysfunction of major organs, known HIV or active chronic hepatitis B or C infection. Histological diagnosis was reviewed by a panel of expert hematopathologists and was available in 97% of the cases.

### staging

The stage of lymphoma was defined by means of physical examination, relevant laboratory parameters (complete blood cell count and basic blood chemistry including 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 and bulky disease was defined as the presence of a tumor mass with a maximal diameter of ≥7.5 cm.

### treatment and dose level allocation

Patients were randomly assigned to receive the currently active dose level of the high-CHOEP-14 or high-CHOEP-21 regimen, respectively at a 1 : 2 ratio. The allocation to a dose level was determined when the patient was randomly allocated to the study (Table 1). The allocated dose level and schedule had to be maintained for all six chemotherapy cycles, unless excessive toxic effects required a dose reduction. In the latter case, the next cycle was given with a dose of one dose level lower. The starting dose level was dose escalation level 1 for patients randomly assigned to the biweekly and dose escalation level 2 for patients randomly assigned to CHOEP-21. Granulocyte colony-stimulating factor (filgrastim or lenograstim) starting on day 4 until recovery of leukocytes was mandatory. Radiotherapy (36 Gy) was given to the sites of primary bulky and extranodal disease.

### sampling and dose escalation strategy

The aim of this study was to estimate the maximum tolerated dose (MTD) separately for the 2-week and 3-week regimens. It was assumed that dose-limiting toxicity (DLT) would be noncumulative and essentially concerned timeliness of the normalization of blood parameters. Therefore, MTD was defined as the maximal dose level at which ≥2/3 of all cycles can be given without DLT and which allowed the timely (i.e. with a maximum delay of 2 days) application of the next cycle of high-CHOEP-14 and high-CHOEP-21, respectively, in order to preserve adherence to the bi- and tri-weekly regimens. DLT was defined as thrombocytopenia <80 000/mm$^3$ or leukocytopenia <2500/mm$^3$ on days 16 and 23 for high-CHOEP-14 and high-CHOEP-21, respectively, or prolonged (>4 days) leukocytopenia <1000/mm$^3$ or thrombocytopenia <20 000/μl, active infection at the end of cycle or serious non-hematological toxicity.

**Table 1.** Dose levels of high-CHOEP regimens

| CHOEP | CHOEP | Dose escalation | | | |
|---|---|---|---|---|---|
| | Baseline | Level 1 | Level 2 | Level 3 | Level 4 |
| Cyclophosphamide (mg/m$^2$) day 1 | 750 | 1000 | 1200 | 1400 | 1600 |
| Doxorubicin (mg/m$^2$) day 1 | 50 | 55[a] | 60[a] | 65[a] | 70[a] |
| Vincristine (mg) day 1 | 2 | 2 | 2 | 2 | 2 |
| Etoposide (mg/m$^2$) days 1–3 | 300 | 375 | 450 | 525 | 600 |
| Prednisone (mg) days 1–5 | 500 | 500 | 500 | 500 | 500 |
| G-CSF | 300/480 | μg s.c. on days 6–13 | | | |

[a]Day 1 + 2.
CHOEP, combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone plus etoposide; G-CSF, granulocyte colony-stimulating factor.

In order to determine the MTD, the up-and-down dose escalation algorithm proposed by Storer [7] was generalized to deal with nonsequential patient entry and toxicity information from multiple cycles per patient. This algorithm had been successfully tested in the bleomycin, etoposide, adriamycin, cyclophosphamide, prednisone, procarbazine (BEACOPP) run-in study of the German Hodgkin Study Group DHSG [8] and enables a rapid and safe dose escalation. Close monitoring of toxic effects by phone interview after each cycle of every single patient as well as rapid dose reductions in the case of toxic events were carried out. The dose level of each newly registered patient was determined according to all available information on all patients treated so far. The dose level was increased for a new patient as soon as two cycles at the currently activated dose level without a DLT had been reported. If a DLT was reported in a cycle at a currently active dose level or below, the next patient was allocated to the next lower dose level. As a consequence of this algorithm, a rapid (and patient sparing) dose finding is possible and an oscillation of the dose level around the MTD, i.e. a dose level with a probability of 33% for a DLT, is achieved promptly. This strategy carries the risk of too high a dose level for 3%–5% of the patients. In order to reduce this risk further, a Bayesian estimator [9] was introduced that did not allow the currently active dose level to be escalated beyond more than one dose level of this estimator. The dose escalation in high-CHOEP-14 and high-CHOEP-21 was evaluated separately in both arms because hematotoxicity in the dose-dense regimen was expected to differ from that in the conventional tri-weekly arm. Since an MTD was expected at a higher dose level for high-CHOEP-21, randomization was carried out in a 2 : 1 fashion between high-CHOPEP-21 and high-CHOEP-14. Recruitment to the respective treatment arm was stopped when a stable (i.e. in 2/3 cycles) DLT was reached. Minimum sample sizes for dose level estimates were determined through simulation studies requiring that the width of the 95% confidence interval for the MTD be in the order of half a dose level ($n = 20$ for high-CHOEP-14 and $n = 40$ for high-CHOEP-21). In order to also obtain estimates for the outcome end points, we planned the trial to recruit at least 50 patients in the treatment arm with the smallest case number.

### end points and assessment of response

Complete remission (CR) and unconfirmed complete remission (CRu) were defined according to the International Workshop criteria [10]. CR and CRu lasting <2 months after the final restaging were counted as progression. Event-free survival (EFS) was defined as the time from the beginning of therapy to disease progression, initiation of salvage therapy, relapse or death whichever come first. Overall survival (OS) was defined as time from the beginning of therapy to death from any cause. Follow-up evaluation included the same investigations and was carried out every 3 months in the first 2 years after treatment, every 6 months from third up to the fifth year after treatment. Statistical analyses were carried out with SPSS (version 11.5).

## results

### patient characteristics

From February 1998 to June 2000, 54 institutions recruited 139 patients for this study. Twenty patients were excluded from further analysis after initial registration for the following reasons: histopathology not according to inclusion criteria (e.g. Burkitt lymphoma, lymphoblastic lymphoma, concomitant follicular lymphoma) ($n = 13$), bone marrow infiltration >25% ($n = 1$), withdrawal of informed consent after initial signature ($n = 2$), severe comorbidities ($n = 2$), previous treatment ($n = 1$) and ECOG performance status of four ($n = 1$). The characteristics of the 119 assessable patients are shown in Table 2. More than two-thirds had an elevated LDH and bulky disease, respectively. In all, 47% of the patients had a high-intermediate or high-risk score according to the age-adjusted IPI. Due to the arm allocation procedure and the nature of this trial, arms were not balanced with respect to risk factors, with a higher percentage of high-risk patients in the high-CHOEP-14 arm. According to the reference pathology which was available in 97.5% of the patients, 11.3% of the aggressive lymphomas were of T-cell origin and 88.7% were of B-cell origin, the majority (73.9%) being diffuse large B-cell lymphomas (DLBCLs) (Table 2).

### dose level allocation and schedule adherence

Forty-seven patients were randomly allocated to high-CHOEP-14 and 92 to high-CHOEP-21. The allocation of the patients to the different dose escalation levels and the evolution of the dose escalation are shown in Table 3 and Figure 1, respectively. Median treatment duration for six cycles was 78 (planned 71) days in high-CHOEP-14 and 108 (planned 105) days in high-CHOEP-21. Treatment duration was calculated excluding patients who received only one cycle and censoring those with early termination of planned treatment because of insufficient response using the Kaplan–Meier method. With respect to the different dose escalation levels, treatment duration was 74 days in high-CHOEP-14 at dose escalation level 1 and 83 days at dose escalation level 2. In the high-CHOEP-21 arm, patients at dose escalation level 4 had a median duration of 108 days. One of the key criteria for the definition of the MTD was the possibility to start the next cycle in the planned 14- or 21-day intervals at each dose level with a tolerance of 2 days, i.e. day 16 for high-CHOEP-14 and day 23 for high-CHOEP-21. Active infections, prolonged neutropenia or thrombocytopenia <20 000 platelets during the

**Table 2.** Clinical characteristics of 119 evaluable patients treated with high-CHOEP

| | All patients ($n = 119$) | High-CHOEP-14 ($n = 41$) | High-CHOEP-21 ($n = 78$) |
|---|---|---|---|
| Gender | | | |
| Male | 74 | 25 | 49 |
| Female | 45 | 16 | 29 |
| Age (years): median (range) | 45 (20–60) | 45 (21–60) | 43 (20–60) |
| LDH > Upper normal value | 69.7% | 70.7% | 69.2% |
| Performance status (ECOG) >1 | 15.1% | 26.8% | 9.0% |
| Stage III/IV | 52.1% | 63.4% | 46.2% |
| Age-adjusted IPI | | | |
| IPI 0 | 20.2% | 22.0% | 19.3% |
| IPI 1 | 32.7% | 14.6% | 42.3% |
| IPI 2 | 37.0% | 43.9% | 33.3% |
| IPI 3 | 10.1% | 19.5% | 5.1% |
| Bulky disease (≥7.5 cm) | 61.3% | 63.4% | 60.3% |
| B symptoms | 45.4% | 41.5% | 47.4% |
| Extranodal disease | 53.8% | 63.4% | 48.7% |
| Extranodal disease >1 | 24.4% | 34.1% | 19.2% |
| Histopathology | | | |
| B-cell lymphomas | 102 (88.7%) | 37 (94.9%) | 65 (85.5%) |
| Diffuse large B cell | 85 (73.9%) | 31 (79.5%) | 54 (71.1%) |
| Centroblastic diffuse | 48 | 15 | 33 |
| Monomorphic | 6 | 0 | 6 |
| Multilobulated | 1 | 0 | 1 |
| Polymorphic | 19 | 8 | 11 |
| NOS | 22 | 7 | 15 |
| Immunoblastic | 8 | 5 | 3 |
| Anaplastic large cell | 5 | 2 | 3 |
| T-cell rich B-cell lymphoma | 1 | 0 | 1 |
| Primary mediastinal sclerosing | 16 | 7 | 9 |
| NOS | 7 | 2 | 5 |
| Centroblastic follicular | 4 | 0 | 4 |
| Centroblastic follicular and diffuse | 2 | 2 | 0 |
| Blastic mantle cell (centrocytoid) | 1 | 0 | 1 |
| High-grade Burkitt like | 1 | 0 | 1 |
| Blastic marginal zone (monozytoid) | 2 | 0 | 2 |
| NOS | 3 | 1 | 2 |
| No subclassification (technical reasons) | 4 | 3 | 1 |
| T-cell lymphomas | 13 (11.3%) | 2 (5.1%) | 11 (14.5%) |
| Anaplastic large cell T/NOS | 8 | 1 | 7 |
| Peripheral | 2 | 1 | 1 |
| Angioimmunoblastic lymphoma type | 1 | 0 | 1 |
| Cytotoxic T- or NK-cell type | 1 | 0 | 1 |
| NOS | 1 | 0 | 1 |
| Insufficient/no material | 4 | 2 | 2 |

CHOEP, combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone plus etoposide; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; NOS, not otherwise specified; NK, natural killer.

previous cycle were counted as unacceptable toxicity. The percentage of cycles with unacceptable toxicity increased in the last three cycles of treatment mainly due to cumulative thrombocytopenia (data not shown).

**Table 3.** Allocation of patients to treatment arms and dose levels

| | High-CHOEP-14 ($n = 47$) | High-CHOEP-21 ($n = 92$) |
|---|---|---|
| Dose level 1 | $n = 17$ | $n = 3$ |
| Dose level 2 | $n = 26$ | $n = 5$ |
| Dose level 3 | $n = 4$ | $n = 15$ |
| Dose level 4 | – | $n = 69$ |

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

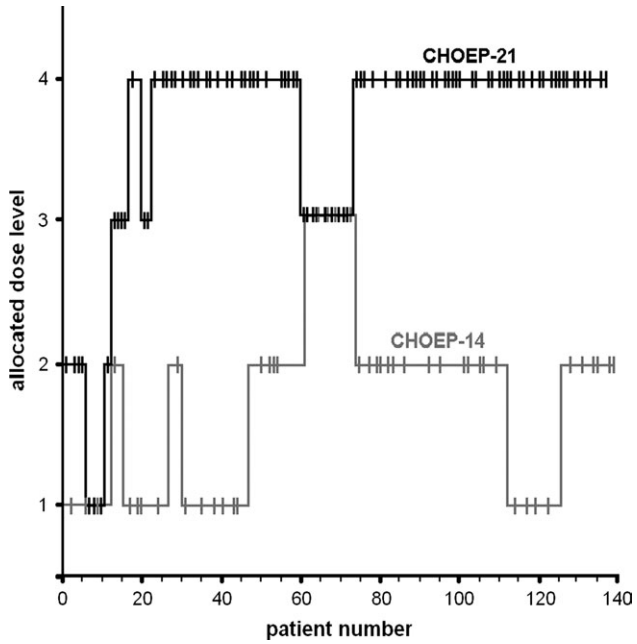


**Figure 1.** Evolution of the dose escalation study for high combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone plus etoposide (CHOEP)-14 and high-CHOEP-21.

## safety and toxicity

High-CHOEP was associated with increased hematotoxicity compared with the baseline CHOEP-21 or CHOEP-14 regimen, respectively [1]. Frequencies of leukocytopenia and thrombocytopenia are shown in Table 4; due to the longer time available for hematopoietic recovery, the dose escalation level reached in high-CHOEP-21 was higher than in high-CHOEP-14. Red blood cell transfusions were given in 42.1% and 32.7% of the cycles after high-CHOEP-14 and high-CHOEP-21, respectively. The respective figures for platelet transfusion were 6.8% and 12.5%, respectively. Higher doses of chemotherapy necessitated more transfusion of platelets and red blood cells than in baseline CHOEP.

The allocated treatment was terminated early in six patients randomly allocated to high-CHOEP-14, because of disease progression or insufficient response in four patients, of whom three received high-dose chemotherapy subsequently; in two patients planned additional radiotherapy of bulky disease was not given after completing chemotherapy (one patient each because of the patient's and the treating physician's decision, respectively). In high-CHOEP-21, treatment was not completed as planned in 12 patients: due to disease progression or insufficient response in seven patients (of whom two proceeded to high-dose chemotherapy with stem-cell support) or excessive toxicity (one patient with viral encephalitis), and planned radiotherapy after the completion of chemotherapy was not given to three patients (one patient because of the patient's and two because of the treating physician's decision, respectively). One patient was taken off study after the fourth cycle due to insufficient compliance (drug addiction). Infections of WHO grades 3 and 4 occurred in 5.9% of the high-CHOEP-14 cycles in 7 of 38 (18.4%) patients and in 2.6% of the high-CHOEP-21 cycles in 10 of 76 (13.2%) patients. Polyneuropathy of the WHO grades 3 and 4 occurred in 5.3% of the patients receiving high-CHOEP-14 and in 1.3% of the patients receiving high-CHOEP-21. There was no treatment-related death after high-CHOEP-14 and one death (1.3%) due to infection after high-CHOEP-21.

With a median follow-up of 48 months for all patients, six secondary neoplasias were reported, four after high-CHOEP-21 and two after high-CHOEP-14. The secondary neoplasias consisted of one acute and two chronic myeloid

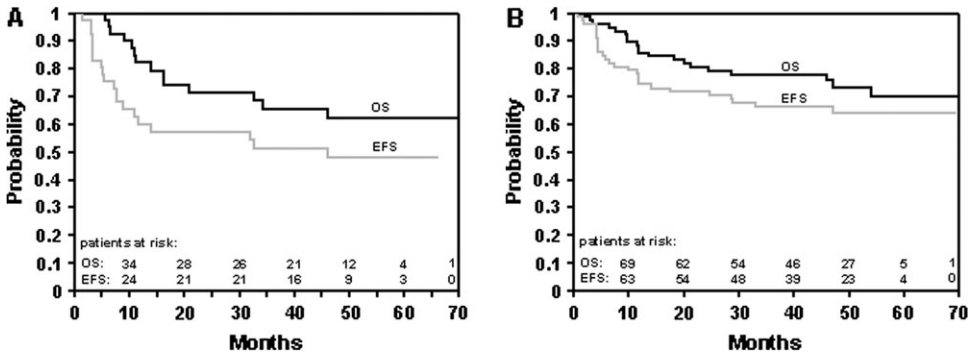


**Figure 2.** Event-free survival (EFS) and overall survival (OS) of 41 assessable patients treated with high-CHOEP-14 (A) and 78 assessable patients treated with high-CHOEP-21 (B).

**Table 4.** Toxicity World Health Organization grades 3 and 4 of high-CHOEP-14 and high-CHOEP-21

| | % of cycles for high-CHOEP-14/ high-CHOEP-21 | | | |
|---|---|---|---|---|
| | Dose level 1 | Dose level 2 | Dose level 3 | Dose level 4 |
| Leukocytes $<2 \times 10^3$/mm$^3$ | 78.4/70.0 | 84.3/84.6 | 100.0/96.9 | –/95.5 |
| Platelets $<50 \times 10^3$/mm$^3$ | 30.0/0.0 | 57.9/88.8 | 75.0/79.4 | –/73.9 |
| Grade 3/4 infections | 6.5/0.0 | 2.6/4.5 | 33.3/1.5 | –/2.8 |
| Grade 3/4 mucositis | 1.3/0.0 | 3.5/13.6 | 0.0/2.9 | –/7.6 |

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

leukemias, one T-cell lymphoma, one basalioma and one liver metastasis of an adenocarcinoma of unknown origin.

### maximum tolerated dose

The MTD for high-CHOEP-14 was reached at dose escalation level 2, with leukocytopenia WHO grades 3 and 4 occurring in 84.3% and thrombocytopenia WHO grades 3 and 4 in 57.9% of the cycles given at this dose level. The MTD for high-CHOEP-21 was reached at dose escalation level 4, with leukocytopenia WHO grades 3 and 4 occurring in 95.5% and thrombocytopenia WHO grades 3 and 4 in 73.9% of the cycles given at this dose level. After the decision was made to use high-CHOEP-21 as the experimental arm in the subsequent multicenter randomized comparison with CHOEP-21, additional patients were treated at this dose level in order to gain more experience with high-CHOEP-21 (Figure 1).

According to the concept of relative dose intensity [3], the MTD of the biweekly CHOEP-14 (at dose escalation level 2) compared favorably with the tri-weekly schedule dose level 4. Compared with baseline CHOEP-21, the relative dose intensity of high-CHOEP-14 at the MTD level 2 (cyclophosphamide 240%, doxorubicin 180%, etoposide 225%, vincristine 150% and prednisone 150%) was 185% compared with 150% for high-CHOEP-21 at dose escalation level 4 (cyclophosphamide 213%, doxorubicin 140%, etoposide 200%, vincristine 100% and prednisone 100% of baseline CHOEP-21). In contrast, according to the concept of 'effective dose' [4], high-CHOEP-21 at dose escalation level 4 had a better effective dose than high-CHOEP-14 at dose escalation level 2 (36.5 versus 33.2 effective dose units).

### efficacy

Due to the nature of the arm allocation and the resulting imbalance of prognostic factors in this randomized phase I/II feasibility design, no statistical calculations for arm comparisons were planned. With high-CHOEP-21, 63 of 78 (80.8%) patients assessable for response achieved a CR, 7.7% a partial remission, 1.3% a minor response, while 9.0% had progressive disease under treatment. After high-CHOEP-14, 27 of 41 (65.8%) achieved a CR and 12.2% a partial remission; 2.4% had no change and 17.1% had progression under therapy. After a median observation time of 48 months, both EFS and OS rates were superior after high-CHOEP-21 compared with high-CHOEP-14 (Figure 2). Four-year EFS was 47.9% after high-CHOEP-14 and 66.2% after high-CHOEP-21, and 4-year OS was 62.1% after high-CHOEP-14 and 73.4% after high-CHOEP-21, respectively. In a multivariate analysis with the variables high-CHOEP-14 versus high-CHOEP-21, elevated LDH, advanced stage III and IV and ECOG performance status of more than or equal to two, there was no difference between high-CHOEP-14 and high-CHOEP-21 with respect to EFS (relative risk: 0.68; $P = 0.222$) and OS (relative risk: 0.74; $P = 0.423$).

## discussion

In the NHL-B1 trial of young good prognosis patients with aggressive lymphoma, the addition of etoposide to the CHOP regimen resulted in a higher rate of CRs, a reduced rate of progressions during therapy and a 10% improvement of EFS after 5 years in young patients with good prognosis aggressive lymphoma. Thus, CHOEP represented the first improvement for this group of patients since the introduction of the CHOP regimen 31 years ago [11]. To date, other attempts to improve treatment results by increasing dose or dose intensity in young good-risk patients have failed [12]. Moreover, in contrast to other dose intensifications of CHOP [13] no increase in secondary myelodysplastic syndromes and acute myeloid leukemias was observed after CHOEP. In the NHL-B1 trial, interval reduction of the CHOEP regimen from 3 to 2 weeks had an (albeit minor) additional positive effect, and in contrast to CHOEP-21 did not only improve EFS (as did CHOEP-21) but also the rate of CRs and OS compared with CHOP-21. Moreover, a subgroup analysis of the NHL-B1 trial showed that patients with bulky disease have a particular benefit from interval reduction. Because the high-CHOEP phase II trial reported here included all young patients with aggressive lymphoma irrespective of their age-adjusted IPI and pretreatment LDH levels, it was the aim of this study to define the MTD both for the biweekly and tri-weekly CHOEP schedule in order to determine which schedule would allow for a higher relative dose intensity or effective dose, thereby qualifying as the comparator in a subsequently planned randomized comparison with baseline CHOEP-21.

The strategy of dose escalation pursued in this study followed a generalized up-and-down dose escalation algorithm as proposed by Storer [7] to deal with nonsequential patient entry and delayed toxicity information due to multiple cycles given at one dose level. This algorithm had been successfully tested in the BEACOPP run-in study of the German Hodgkin Study Group (DHSG) [8]. The experience of the DHSG in that trial and the results of the high-CHOEP dose escalation study confirm that this algorithm enables a rapid and safe escalation.

The course of the high-CHOEP dose escalation and the DLTs confirmed our assumption that the DLT would be defined by myelosuppression (i.e. leukocytopenia or thrombocytopenia) and not by other toxic effects and that higher doses should be feasible in the tri-weekly compared with the biweekly regimen. The results of our dose escalation study demonstrate that both with CHOEP-14 and CHOEP-21 significant dose escalations

are possible without the risk of encountering undue toxic effects. This is also supported by only one therapy-associated death occurring in this prospective study with 119 assessable patients.

That higher total doses can be achieved with dose-escalated CHOEP-21 does not necessarily mean that high-CHOEP-21 at dose escalation level 4 is more efficacious than high-CHOEP-14 at dose escalation level 2. Several models have been indicated to predict and compare the efficacy of different chemotherapy regimens [14–16]. Of the more recent models, the concepts of relative dose intensity [3] and effective dose [4], which had correctly predicted the results of the dose-escalated BEACOPP regimen in Hodgkin's lymphoma [8], have received much attention. Applying both models to the MTD of six cycles of CHOEP-14 given at dose escalation level 2 and high-CHOEP-21 at dose escalation level 4, different predictions, however, emerge with respect to their relative efficacy. The concept of relative intensity dose clearly favors high-CHOEP-14 at dose escalation level 2 over high-CHOEP-21 at dose escalation level 4, which have relative dose intensities of 185% and 151%, respectively, compared with baseline CHOEP-21. In contrast, the calculation according to the effective dose concept favors high-CHOEP-21 at dose level 4. According to this concept, six cycles of high-CHOEP-14 at dose level 2 have an effective dose of 33.2 U compared with baseline CHOEP-21 (effective dose: 22.4 U) and should improve the rates of CRs from 67.0% (CHOEP-21 baseline) to ~76.0%, while the model predicts 36.5 effective dose units for six cycles of high-CHOEP-21 at dose level 4 which according to this concept should result in a slightly higher CR rate of 78%. This together with the higher total dose achievable with high-CHOEP-21 compared with high-CHOEP-14 made us choose high-CHOEP-21 for comparison with baseline CHOEP-21 in a subsequent randomized trial which aimed at improving further the results in young patients with good prognosis DLBCL. Dose level 3, rather than MTD dose level 4 of high-CHOEP-21, was chosen as the 'maximal practible dose' for this nationwide trial, in which centers with less experience than those in this dose escalation study were to participate. The results of this randomized trial will show whether the predicted 11% increase in CRs will be achieved in real life and whether the concept of effective dose will stand clinical scrutiny.

## funding

Deutsche Krebshilfe e.V.

## acknowledgements

Data management team: B. Mann, U. Schönwiese, L. Martin Montanez, C. Schorpp, T. Rixecker; Database: M. Kunert, B. Wicklein; Biometry: ML, M. Klöss, DH. The following investigators and institutions recruited patients for this study: Universitätsklinikum Münster, Münster—W. E. Berdel; Universitätsklinikum Magdeburg, Magdeburg—MM; Städtisches Klinikum, Karlsruhe—MB; Universitätsklinikum des Saarlandes, Homburg—MP; Krankenhaus Maria-Hilf II Franziskushaus, Mönchengladbach—UG; Helios-Klinikum Bad Saarow/Fürstenwalde, Bad Saarow—UW; Krankenanstalten Mutterhaus der Borromäerinnen, Trier—M. R. Clemens; Klinikum der Stadt Ludwigshafen, Ludwigshafen—MH; Städtische Kliniken, Oldenburg—BM; Klinikum der Universität München Innenstadt, München—F. Oduncu; St-Antonius-Hospital, Eschweiler—R. Fuchs; Krankenhaus Nordwest Frankfurt, Frankfurt—E. Jäger; Universitätsklinikum Bochum, Knappschaftskrankenhaus, Bochum—W. Schmiegel; Universitätsklinikum Marburg, Marburg—A. Neubauer; Krankenhaus der Barmherzigen Brüder, Trier—C. B. Kölbel; Universitätsklinikum Eppendorf, Hamburg—C. Bokemeyer; Klinikum der Stadt, Villingen-Schwenningen—W. Brugger; GMP Dres. med. Otremba/Reschke/Hinrichs, Oldenburg—B. Otremba; Krankenhaus der Barmherzigen Brüder, Regensburg—E.-D. Kreuser; Klinikum Großhadern der LMU, München—W. Hiddemann; GMP Dres. med. Abenhardt/Bojko/Bosse/Riedner München—D. Bosse; Kaiserswerther Diakonie, Düsseldorf—J. Kraft; Rotes Kreuz Krankenhaus, Kassel—C. Löser; Klinikum Region Hannover—Krankenhaus Siloah, Hannover—H. Kirchner; Kreiskrankenhaus Waldbröl, Waldbröl—S. Brettner; Universitätsklinikum Leipzig, Leipzig—D. Niederwieser; Medizinische Hochschule, Hannover—A. Ganser; Krankenhaus Altstadt, Magdeburg—E. Kettner; St-Lukas-Klinik, Solingen—K.-H. Beckers; Universitätsklinikum Rostock, Rostock—M. Freund; Kreiskrankenhaus Neumarkt, Neumarkt—F. Tympner; Krankenhaus Hohe Warte/Klinikum Bayreuth, Bayreuth—M. Strotzer; GMP Dres. med. Weidenbach/Balser Marburg—F. Weidenbach; Krankenhaus Tutzing—H. P. Schobel; Städtisches Klinikum, Fulda—H.-G. Höffkes; Robert-Koch-Krankenhaus, Gehrden—J. Brücher; Praxis für Hämatologie und Onkologie, Regensburg—R. Dengler; GMP Dres. med. Czerwonski/Freier, Hildesheim—W. Freier; Klinikum Hoyerswerda, Hoyerswerda—K. Gasiorek; Kliniken der Stadt Köln, Krankenhaus Merheim, Köln-Merheim—E. Stoelben; Diakoniekrankenhaus Schwäbisch Hall—T. Geer; Kreiskrankenhaus Am Plattenwald, Bad Friedrichshall—D. Bürkle; Franz-Hospital Dülmen, Dülmen—G. Dresemann; St Vincenz-Krankenhaus, Limburg—K.-P. Schalk; Katharinenhospital, Stuttgart—H. G. Mergenthaler; Städtische Kliniken, Darmstadt—D. Fritze; Leopoldina-Krankenhaus, Schweinfurt—S. Kanzler; Klinikum Rostock Südstadt, Rostock—B. Krammer-Steiner; Caritas-Krankenhaus, Lebach—S. Kremers; Klinikum Minden, Minden—H. Bodenstein; Universitätsklinik Köln, Köln—M. Hallek; Klinikum Kreis Herford, Herford—U. Schmitz-Huebner.

## references

1. Pfreundschuh M, Trumper L, Kloess M et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood 2004; 104: 626–633.
2. Pfreundschuh M, Truemper L, Oesterborg A et al. CHOP-like chemotherapy plus rituximab compared with CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large B-cell lymphoma: a randomized controlled trial by the Mabthera International Trial (MInT) Group. Lancet Oncol 2006; 7: 379–391.
3. Meyer RM, Hryniuk WM, Goodyear MD. The role of dose intensity in determining outcome in intermediate-grade non-Hodgkin's lymphoma. J Clin Oncol 1991; 9: 339–347.

4. Hasenclever D, Brosteanu O, Gerike T et al. Modelling of chemotherapy: the effective dose approach. Ann Hematol 2001; 80: B89–B94.
5. Harris NL, Jaffe ES, Diebold J et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 1999; 17: 3835–3849.
6. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329: 987–994.
7. Storer BE. Design and analysis of phase I clinical trials. Biometrics 1989; 45: 925–937.
8. Tesch H, Diehl V, Lathan B et al. Moderate dose escalation for advanced stage Hodgkin's disease using the bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone scheme and adjuvant radiotherapy: a study of the German Hodgkin's Lymphoma Study Group. Blood 1998; 92: 4560–4567.
9. O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. Biometrics 1990 46: 33–48.
10. Cheson BD, Horning SJ, Coiffier B et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999; 17: 1244.
11. McKelvey EM, Gottlieb JA, Wilson HE et al. Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. Cancer 1976; 38: 1484–1493.
12. Tilly H, Mounier N, Lederlin P et al. Randomized comparison of ACVBP and m-BACOD in the treatment of patients with low-risk aggressive lymphoma: the LNH87-1 study. Groupe d'Etudes des Lymphomes de l'Adulte. J Clin Oncol 2000; 18: 1309–1315.
13. Shipp MA, Neuberg D, Janicek M et al. High-dose CHOP as initial therapy for patients with poor-prognosis aggressive non-Hodgkin's lymphoma: a dose-finding pilot study. J Clin Oncol 1995; 13: 2916–2923.
14. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep 1979; 63: 1727–1733.
15. Skipper HE, Schabel FM Jr. Spontaneous AK leukemia (lymphoma) as a model for human leukemias and lymphomas. Cancer Chemother Rep 3 1972; 3: 3–5.
16. Norton L, Simon R. Tumor size, sensitivity to therapy, and design of treatment schedules. Cancer Treat Rep 1977; 61: 1307–1317.