Original article

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Practicability and acute haematological toxicity of 2- and 3-weekly CHOP and CHOEP chemotherapy for aggressive non-Hodgkin's lymphoma: results from the NHL-B 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: There is evidence that intensified variants of the classical 3-weekly CHOP-21 chemotherapy [cyclophosphamide (C), doxorubicin (H), vincristine (O), prednisone (P)] may improve treatment outcome in aggressive lymphoma. Three variants using either an addition of etoposide (CHOEP-21: 100 mg/m^2 on days 1–3), the shortening to 2-week intervals using recombinant human granulocyte colony-stimulating factor (rhG-CSF; CHOP-14) or both (CHOEP-14) are currently compared with CHOP-21 in the NHL-B trial of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). To enable more extensive testing of these schemes we here characterise their practicability regarding schedule adherence, acute haematotoxicity and need for supportive treatment.

Patients and methods: The trial included patients with normal lactate dehydrogenase (LDH) aged ≤60 years (NHL-B1) and patients aged 61–75 years (NHL-B2). The data are taken from an interim analysis. Data from 959 patients (CHOP-21: 232; CHOP-14: 238; CHOEP-21: 244; CHOEP-14: 245) from 162 institutions with a total of 5331 therapy cycles were evaluated.

Results: The dose adherence in the NHL-B1 trial was excellent. The median relative dose (RD; i.e. actually given compared to planned dose) exceeds 98% for the myelosuppressive drugs in all four regimens. Only ≤5% of patients received a relative dose <80% (RD <80). The median treatment duration could be shortened as scheduled for both CHOP-14 by 36 days and CHOEP-14 by 35 days. The dose adherence in the NHL-B2 trial was excellent for CHOP-21 and CHOP-14 for the myelosuppressive drugs (median RD ≥98%, RD <80 ≤15%). Addition of etoposide, however, was accompanied by more dose erosion (median RD ≥97%, RD <80 ≤17% for CHOEP-21 and ≤27% for CHOEP-14). The median treatment duration could be shortened by 34 days with CHOP-14 compared with CHOP-21. Less treatment shortening was feasible for CHOEP-14 compared with CHOP-21 (median of 29 days). CHOP-14 and CHOP-21 were similar regarding toxicity profile, rate of infection, use of antibiotics, rate of transfusions and hospitalisation. CHOEP schemes were associated with a higher rate of infections, more transfusion requirements, more antibiotic use and longer hospitalisation than the CHOP schemes, particularly in patients aged >60 years. Haematopoietic recovery was age- and treatment-related.

Conclusions: CHOP-14 with the addition of rhG-CSF is safe and practicable in a large multicentre setting in patients aged 18–75 years. Despite shorter treatment intervals it can be delivered at the same dose as the classical 3-weekly CHOP with a comparable toxicity profile. The addition of etoposide is feasible and safe for patients ≤60 years old in both the CHOEP-21 and CHOEP-14 schemes. For patients >60 years of age the addition of etoposide is associated with marked dose erosion due to increased toxicity. In this age group CHOEP should be used with caution.

Key words: aggressive lymphomas, CHOP regimen, clinical study, relative dose toxicity

Introduction

Since the introduction of the 3-weekly CHOP chemotherapy 25 years ago [1] many efforts have been undertaken to improve the efficacy of multicycle polychemotherapy for patients with aggressive lymphoma. A variety of regimens was invented by adding

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further cytotoxic drugs or modifying their dose, and many of these regimens were suggestive for a better outcome in non-randomised trials [2–7]. However, when tested in a large prospective randomised trial comparing the novel schemes m-BACOD, ProMACE-CytaBOM and MACOP-B with CHOP no relevant difference in efficacy was found between these regimens. As toxicity was lowest for the 3-weekly CHOP regimen it is considered as the gold standard chemotherapy for aggressive lymphoma [8].

In 1993 the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) decided to investigate in a large multicentre randomised phase III trial whether specific intensifications of the classical 3-weekly CHOP scheme could improve long-term treatment outcome. Two methods of intensification were considered. One was the addition of a presumably potent cytotoxic substance to the CHOP scheme without modifying dosing and timing of the other components. The drug selected was etoposide, because of data indicating a relevant activity in aggressive lymphoma. Furthermore, a phase II trial had previously shown feasibility of the CHOEP scheme (CHOP plus etoposide 100 mg/m^2 on days 1–3) in a multicentre setting and suggested promising tumour control in previously untreated patients [9].

The second method of intensification, so far not investigated in a large-scale trial, was the shortening of the time intervals of the CHOP regimens. In rapidly growing tumours shortening treatment intervals should considerably impair tumour regrowth between the treatment cycles. To obtain an idea of the potential magnitude of this effect we performed biomathematical model calculations applying a model used for designing an intensified regimen for advanced stage Hodgkin's disease [10–12]. This model predicted that shortening treatment intervals from 3 weeks to 2 weeks should lead to an improvement in long-term treatment outcome (i.e. time-to-treatment failure, TTF) in the order of ≥10%. Such a difference was considered to be clinically relevant and detectable in a sufficiently large phase III trial. To support recovery of granulocytes it was decided to include recombinant human granulocyte colony-stimulating factor (rhG-CSF) in the 2-week regimens from days 4 to 13.

In 1993 the DSHNHL activated the multicentre randomised phase III trial called NHL-B (Figure 1). Four treatment options were compared in a 2 × 2 factorial design. CHOP chemotherapy was planned to be given in 21-day intervals without rhG-CSF (CHOP-21) or in 14-day intervals with the addition of rhG-CSF (CHOP-14). Two further treatment arms resulted from the addition of etoposide (CHOEP-21 and CHOEP-14). The trial was formally split into two trials as two different groups of patients were enrolled. One trial (NHL-B1) included patients ≤60 years of age with a low-risk profile [lactate dehydrogenase (LDH) below the upper normal value). The second trial (NHL-B2) included patients between 61 and 75 years of age irrespective of the risk profile. Patients ≤60 years of age with an elevated LDH value were included in a different trial of the study group (NHL-A), comparing conventional CHOEP-21 with a strategy including high-dose chemotherapy and autologous bone marrow transplantation [13].

Recruitment for the two trials was terminated in July 2000. The last interim analysis has indicated a benefit of the time-shortened

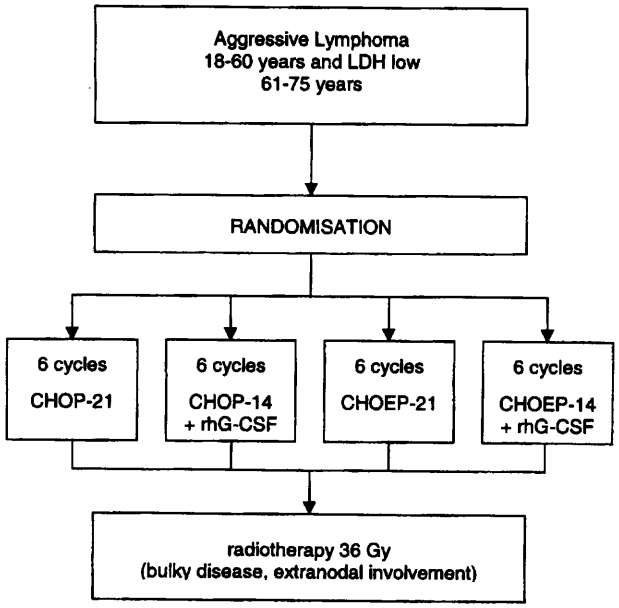


Figure 1. Study design for the NHL-B1 and NHL-B2 trials.

CHOP-14 scheme in the older age group (NHL-B2) and a benefit of etoposide in the younger age group (NHL-B1) [14, 15]. Final analyses on treatment outcomes of all 1500 randomised patients are expected for 2003.

It is the objective of this report to describe in detail the practicability of the four CHOP variants by analysing how well the intended schedules could be applied, to what extent dose erosion occurred and what spectrum of dose-limiting toxicities occurred. As the NHL-B trial was conducted in a multicentre setting with a broad spectrum of participating institutions this analysis should provide important information for wider use of the new schemes.

Patients and methods

Study design

Histologically proven untreated high-grade non-Hodgkin's lymphomas according to the KIEL classification were included [16]. Translated into the novel revised European–American lymphoma (REAL) classification the following entities were included [17]: diffuse large B-cell lymphoma, follicular centre lymphoma grade 3, Burkitt's lymphoma, Burkitt-like lymphoma, blastic variants of mantle cell lymphoma, primary mediastinal large B-cell lymphoma, aggressive marginal lymphomas, anaplastic T/null cell lymphoma, precursor lymphoblastic lymphoma, peripheral T-cell lymphoma not otherwise specified and angioimmunoblastic T-cell lymphoma. A panel of five reference pathologists was established and primary pathologists were requested to submit material to one of the panel members for review. The reference pathologists classified each lymphoma according to KIEL and REAL classifications. About 95% of all cases were reviewed.

Patients aged 18–60 years were only included if the pretreatment LDH value had not exceeded the upper normal value of the local laboratory (NHL-B1 trial). Patients aged between 61 and 75 years were included irrespective of LDH values (NHL-B2 trial). Exclusion criteria were presence of a second tumour, previous chemo/radiotherapy, severe concomitant disease or organ dysfunction, bone marrow involvement with >25% lymphoma cells, HIV infection, initial white blood cell (WBC) count <3 × 10^3/mm^3, initial platelet level <100 × 10^3/mm^3, a World Health Organisation (WHO) performance

status of 4 and reduced patient compliance. The protocol was approved by the local ethics review committees responsible for the participating centres. The staging procedure involved the following mandatory examinations: clinical examination, laboratory investigations, chest X-ray, abdomen sonography, CT of chest and abdomen, bone marrow biopsy. Written informed consent was requested.

A 2 × 2 factorial study design was implemented for both the NHL-B1 and NHL-B2 trials. In Figure 1 both are shown together. The primary end point of the trial is time-to-treatment failure (TTF) which is defined as time elapsed from the first day of treatment to progression, failure to achieve a complete response/unconfirmed complete response (CR/CRu) at termination of protocol treatment, initiation of an alternative treatment, relapse or death, whichever comes first. The trial was set up to detect a 30% reduction of the hazard rate of the primary end point separately in the groups of patients aged 18–60 years and 61–75 years. We planned to randomise a minimum of 700 eligible patients into each of the two trials.

The CHOP scheme was defined as cyclophosphamide [750 mg/m^2 intravenously (i.v.)], doxorubicin (50 mg/m^2 i.v.), vincristine (2 mg i.v.) all given on day 1 and prednisone (100 mg/day per os) given on days 1–5. In the CHOEP regimen the same dosage is used for cyclophosphamide, doxorubicin, vincristine and prednisone. Etoposide was given in a dose of 100 mg/m^2 i.v. on days 1–3. All patients were planned to receive six cycles of chemotherapy. In case of progression of the disease during treatment or in case of insufficient response (no change/minor response) at the time of interim restaging after three cycles of chemotherapy, switching to a salvage therapy was recommended. Planned treatment was continued without any dose reduction if the WBC count was >2.5 × 10^3/mm^3 and if platelets were >80 × 10^3/mm^3 on day 1 of the next intended cycle. In case these threshold values were not exceeded, physicians were advised to wait and control the WBC count and platelets up to 1 week and give full dose treatment as soon as the criteria were met. A dose reduction of 25% for cyclophosphamide, doxorubicin and etoposide was recommended if the WBC count and platelet recovery took >1 week. A 50% reduction for these drugs was recommended if the recovery was delayed by >2 weeks. Support by rhG-CSF was scheduled in the 2-weekly regimens (CHOP-14 and CHOEP-14) from days 4 to 13 (10 day duration) at a dose of 300 μg/day and 480 μg/day for patients <75 kg and ≥75 kg body weight, respectively. rhG-CSF was not recommended for the 3-weekly schemes.

After completion of six cycles of chemotherapy, local radiotherapy with 36 Gy was planned for all patients with initial bulky disease or conglomerate tumours (largest diameter ≥7.5 cm) and was recommended for extranodal tumours.

Trial and data management

A total of 1500 eligible patients from 162 centres were randomised into the two trials until June 2000 (NHL-B1: 762; NHL-B2: 738). Of these patients, 39% were treated in university hospitals, 59% in regional hospitals and 2% by private oncological practitioners in Germany and Switzerland (see Acknowledgements).

All data were submitted on case report forms and checked by a physician and data manager. According to standard operating procedures they checked the data for completeness and consistency and initiated queries back to the treating physicians if necessary. Queries were initiated for ~16% of all case report forms. Cleared data were entered into an Oracle 8 (Oracle Corp., Redwood Shores, CA, USA) database via a data entry process with additional checks for consistency. No routine on-site monitoring or source data verification was undertaken.

For the subsequent analysis the following data were used on a per cycle basis: date of cycle start, total dose of each drug given, days of rhG-CSF, number of erythrocyte and platelet transfusions, application and duration of antibiotics, number of days with fever, total number of days of hospitalisation, WBC count, platelet counts, haemoglobin, and occurrence of acute toxicities according to WHO grades [18].

For each patient entering into the analysis a panel (consisting of a physician, statistician and data manager) assessed whether the treatment was given according to protocol. In case of deviation the panel identified the time of and classified the reasons for early treatment termination [tumour-related, excessive toxicity, major protocol violation, patient withdrawal, concomitant disease or other (e.g. accidents)]. For each patient who died the cause of death was retrieved whenever possible.

Patient characteristics

This analysis is based on data obtained in the interim analysis in 2000. At this time point 959 patients had complete information on treatment and treatment outcome. Patient characteristics are listed in Table 1. Due to the different inclusion criteria the risk profile of the two age groups differs. However, with regard to blood counts before the first treatment cycle no differences were observed.

Description of the data set specific for this analysis and statistics

In total 5331 cycles of chemotherapy were given to the 959 patients. Of these, 803 patients (84%) had received all six cycles of chemotherapy. Two-hundred and seventy-five patients received radiation as planned. Early termination of treatment before cycle 6 occurred in 156 patients. Reasons were insufficient tumour response (61 patients), excessive toxicity (69 patients), concomitant disease (three patients), patient withdrawal (16 patients) and protocol violation (seven patients). Protocol violation was defined as a change of chemotherapy or treatment arms or interruption of chemotherapy for >3 weeks, that could not be related to treatment toxicity or ineffective treatment. Data from all treatment cycles until time of treatment interruption or protocol violation were entered into the subsequent analysis. Completeness of data regarding drug doses and duration of therapy cycles was 99.8% and 99.9%, respectively. The total treatment duration was calculated as the total interval from the first day of the first cycle to the last day of the fifth cycle. The planned intervals were 70 days for the 14-day regimens and 105 days for the 21-day regimens. The relative dose (RD) was calculated as the total dose actually given divided by the total dose planned for all six cycles of chemotherapy. To describe time and dose erosion we used cumulative frequency plots which take into account tumour-related treatment interruptions. Technically, inverse Kaplan–Meier plots were used to censor for these treatment interruptions.

Blood count measurements for WBC, platelets and haemoglobin were requested. The treatment protocol recommended two measurements per week, but to account for the multicentre setting no strict rules were imposed to comply with this recommendation. In fact a median number of three blood counts were documented per cycle and treatment arm. In total 17 015 blood counts were documented. To obtain a population description of the blood count time courses over the planned six-cycle treatments aggregate figures were generated with time scales according to protocol treatment (e.g. day 1 of cycle 3 is day 29 in 2-weekly schemes and day 43 in 3-weekly schemes). Thus in these plots data observed on day 15 or later in the CHOP-14 and CHOEP-14 cycles are not considered, and likewise data obtained later than day 21 in the CHOP-21 and CHOEP-21 cycles are not considered. Hence, a total of 15 638 values were entered into generation of the aggregate figures (see below). Using this procedure the median number of measurements obtained for each day was 35 (range 1–91). To describe the observed data we used boxplots with the upper and lower limits describing the 25% and 75% percentiles.

To estimate the independent impact of age and treatment arms on the treatment-related mortality we performed a multivariate analysis using a logistic regression model. To compare protocol adherence between university hospitals and regional hospitals with regard to the supportive treatments and

Table 1. Patient characteristics ($n = 959$)

	Age group (no. of patients)	
	≤60 years ($n = 503$)	>60 years ($n = 456$)
Gender		
Male (%)	63	54
Female (%)	37	46
Age (years)		
Median	48	67
Range	18–60	61–75
Risk factors		
LDH >N[a] (%)	0	48
Stage III/IV (%)	32	53
ECOG >1 (%)	6	23
Extranodal disease >1 (%)	10	21
Age-adjusted IPI		
Low (IPI 0) (%)	65	39
Low–intermediate (IPI 1) (%)	33	37
High–intermediate (IPI 2) (%)	2	18
High (IPI 3) (%)	0	6
B-symptoms (%)	21	35
Bulky disease (%)	28	40
Bone marrow involvement[b] (%)	6	13
Histology		
Diffuse large B-cell lymphoma (%)	63.4	74.0
Other B-cell lymphoma/not specified B-cell lymphoma (%)	22.4	19.7
T-cell lymphoma (%)	13.5	6.1
NOS (%)	0.7	0.2
Blood counts before first cycle (median)		
WBC ($10^3/mm^3$)	7.1	7.1
Platelets ($10^3/mm^3$)	271	280
Haemoglobin (g/dl)	13.7	12.9

[a]Upper normal value.

[b]Bone marrow involvement with >25% lymphoma cells was an exclusion criteria of the study.

ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NOS, not otherwise specified; WBC, white blood cells.

frequency of side-effects we used *t*-test statistics and chi-square test statistics on a significance level of 0.05.

Results

Dose and schedule erosion

Figure 2 gives a comprehensive description of the adherence to protocol in the four treatment arms separately for the two trials (age groups). Regarding patients ≤60 years of age the median treatment duration in all treatment arms almost exactly matched the planned duration of 70 and 105 days, respectively. Shorter treatment durations due to early treatment termination not related to tumour growth were rare (Figure 2A). Figure 2C, E and G illustrates minor dose erosion of cyclophosphamide, doxorubicin and etoposide in patients ≤60 years of age. The median RD is ≥99% for cyclophosphamide, doxorubicin and etoposide. Independent of the treatment arms and drugs only 5% of patients received a relative dose <80% (RD <80; Table 2). Both 2-week regimens (CHOP-14 and CHOEP-14) could be applied with little dose and schedule erosion in patients ≤60 years of age.

Figure 2B provides the schedule data for patients >60 years of age. The intended interval shortening was successful. Treatment was completed 34 days (median) earlier with CHOP-14 compared with CHOP-21. The median duration of the CHOEP-21 scheme is also well controlled. However, 31% of the patients terminated treatment in the CHOEP-21 arm earlier than planned. The corresponding curve for the CHOEP-14 regimen shows even greater deviations from the planned timing. Compared with CHOP-21 the treatment duration of CHOEP-14 could be shortened by 29 days (median).

Figure 2D, F and H provides detailed insight into dose erosion for patients >60 years of age. With regard to the median RD the four regimens reached values >96% of the planned dose. However, the schemes containing etoposide led to a considerable dose erosion of cyclophosphamide and doxorubicin compared with the CHOP schemes. In the CHOP-21 scheme only 7% of the patients received a relative dose of cyclophospamide <80% while in the CHOEP-14 and CHOEP-21 schemes these were 24% and 15%, respectively. Comparing Figure 2G and H shows an important age-dependent dose erosion with regard to etoposide. While only 5% of the younger patients received <80% of the planned etoposide dose, this increased to 17% for CHOEP-21 and 27% for CHOEP-14 in elderly patients.

Deviations from the planned dose of vincristine primarily occurred in the late therapy cycles. Eighty-three per cent of patients ≤60 years of age received full vincristine dose in cycle 6, while this number diminished to 75% for the elderly patients.

rhG-CSF was given regularly in the 2-week schemes. Ninety-five to 100% of the patients received rhG-CSF in the first five cycles of the 2-week regimens in both age groups. In cycle 6, 91% of the patients in the CHOP-14 arm and 94% in the CHOEP-14 arm received rhG-CSF. In the 3-week treatment arms rhG-CSF was not recommended. Among patients ≤60 years of age 6% received rhG-CSF in cycle 5 in the CHOP-21 arm and 15% in the CHOEP-21 arm. For patients >60 years of age 5% received rhG-CSF in cycle 5 in the CHOP-21 arm and 24% in the CHOEP-21 arm. In the 2-week treatment regimens the duration of rhG-CSF reached a median of 10 days.

Haematotoxicity and supportive measures

Figures 3, 4 and 5 describe the time courses of leucocytes, thrombocytes and haemoglobin over the entire treatment period for the four different treatment arms. Figure 3 shows the periodic pattern for leucocytes. In the 3-week schemes the nadir counts occur on days 10–12 of the cycle and on days 8–10 in the 2-week

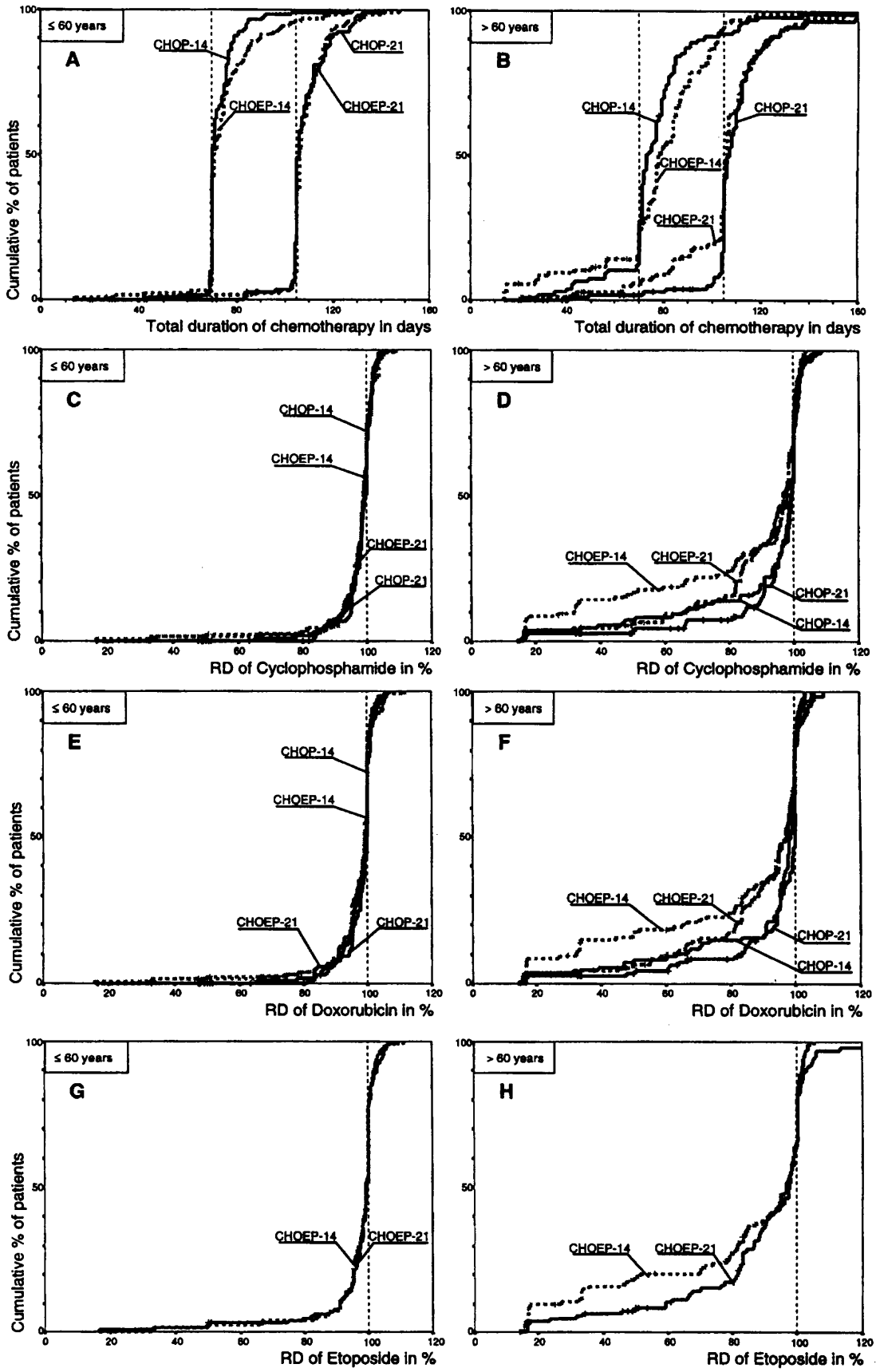


Figure 2. Treatment duration and dose erosion according to treatment arms and age group. Cumulative distribution functions are shown for each treatment arm. Vertical dashed lines indicate the planned values as specified in the protocol.

Table 2. Data for the median and 20% percentiles for treatment duration and the median for the relative dose and relative dose (RD) <80

	CHOP-21	CHOP-14	CHOEP-21	CHOEP-14
Treatment duration (NHL-B1)				
Median duration (days)	106	70	106	71
20% percentile (days)	104	69	104	69
Treatment duration (NHL-B2)				
Median duration (days)	107	73	106	78
20% percentile (days)	104	70	98	69
Relative dose of cyclophosphamide (NHL-B1)				
Median RD (%)	99	100	99	99
RD <80 (%)	0	2	3	2
Relative dose of cyclophosphamide (NHL-B2)				
Median RD (%)	99	99	98	97
RD <80 (%)	7	14	15	24
Relative dose of doxorubicin (NHL-B1)				
Median RD (%)	100	100	99	99
RD <80 (%)	0	2	4	4
Relative dose of doxorubicin (NHL-B2)				
Median RD (%)	98	100	98	97
RD <80 (%)	8	15	17	24
Relative dose of etoposide (NHL-B1)				
Median RD (%)	–	–	99	99
RD <80 (%)	–	–	5	4
Relative dose of etoposide (NHL-B2)				
Median RD (%)	–	–	98	97
RD <80 (%)	–	–	17	27

schemes. Nadir leucocyte counts of successive cycles reached similar values providing no evidence for cumulative toxicity in any treatment arm. In the 2-week schemes a two-peak pattern is observed under rhG-CSF. Immediately after the start of rhG-CSF (i.e. following day 4 in each cycle) a transient increase in WBC count was followed by the nadir; a second overshoot occurred on days 12–14. Nadir counts are generally higher than in 3-weekly CHOP. Furthermore, the second overshoot shows a remarkable variation, which is indicated by the increasing size of the boxes in the aggregated boxplots. Generally lower leucocyte nadir counts were observed in the older age group.

Figure 4 shows platelet time courses. There is generally an oscillatory pattern except for the CHOP-14 regimen in the younger age group. There is an indication of cumulative toxicity with regard to peak values and nadirs in the regimens containing etoposide (particularly in the elderly age group). We observed more pronounced cyclic patterns in elderly patients with lower nadir values, indicating a larger chemosensitivity and a more intensive activation of regulatory processes.

Figure 5 shows the time courses for haemoglobin concentrations. There is cumulative toxicity which differs between the treatment arms. It is minor for the CHOP-21 regimen and most prominent for the CHOEP-14 regimen. It should be noted that these data are biased by red blood cell (RBC) transfusions in later cycles. Table 3 summarises toxicities and toxicity-related supportive measures. Generally, the haematological toxicities and the incidence of infections and mucositis are elevated in patients >60 years of age. Platelet transfusions reached 1% per cycle in the CHOP-14 arm in the elderly patients. Platelet transfusions were more frequent in patients >60 years of age and in etoposide-containing regimens. Furthermore, patients aged >60 years receiving CHOEP-14 required RBC transfusion in 32% of the cycles. Rate of infections and mucositis in patients aged >60 years was between 0–2% (CHOP-schemes) and 2–7% in etoposide-containing schemes. Table 3 also gives the average duration of hospitalisation. Generally the elderly age group required one to three extra days of hospitalisation per cycle compared with the patients aged ≤60 years. The etoposide-containing regimens required on average about 1–3 days more hospitalisation than the CHOP regimens.

Table 4 gives data on treatment-related mortality and second cancers. In total, 30 patients died. In the CHOP-21 arm three patients died of sepsis. In the CHOP-14 scheme six patients died (sepsis: four; ARDS: one; haemorrhagia: one). In the CHOEP-21 treatment arm eight patients died (sepsis, five; heart failure, two; pulmonary embolism, one). In the CHOEP-14 treatment arm

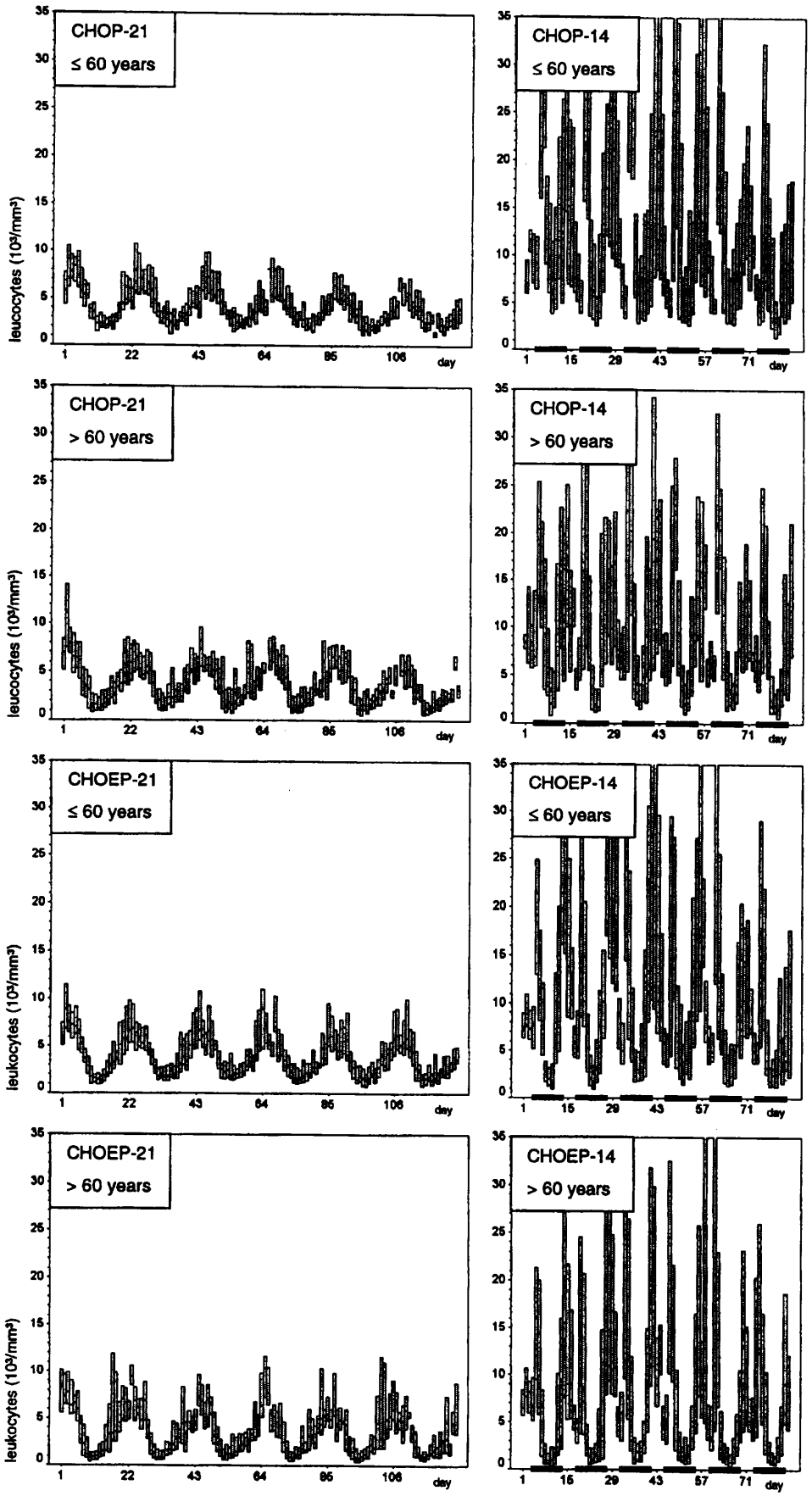


Figure 3. Leucocytes (10^3/mm^3) over the successive therapy cycles.

13 patients died (sepsis, 10; ARDS, one; renal failure, one; liver failure, one).

Death due to treatment-related toxicity during the course of treatment was very rare in patients ≤60 years of age. These numbers were higher for elderly patients.

A logistic regression model was applied to model the probability of treatment-related mortality. Age >60 years was the most prominent adverse prognostic factor ($P = 0.0001$). Compared with CHOP-21 only CHOEP-14 was associated with a significant risk increase ($P = 0.02$).

In a median observation time of 34 months 14 secondary cancers have been observed so far. There was no association with treatment arms.

Centre effect

No significant differences could be detected with regard to toxicity-related mortality comparing university hospitals and regional hospitals ($P = 0.280$). Furthermore, no differences with regard to rate of infection ($P = 0.991$), use of platelet ($P = 0.740$) and RBC transfusion ($P = 0.450$) were seen between these institutions. We found, however, that hospitalisation for regional hospitals lasted 1 day longer and that they had a more extensive use of antibiotics ($P < 0.001$).

Discussion

As recent interim analyses of the NHL-B trial have indicated, the intensified variants of the classical 3-weekly CHOP-21 regimen are effective chemotherapies for aggressive lymphoma [14, 15]. In particular, the 2-weekly CHOP-14 regimen has the potential of being superior to the present 3-weekly CHOP scheme for patients >60 years of age (NHL-B2), while the addition of etoposide in CHOEP schemes seems to improve treatment outcome for younger patients with low-risk profile (NHL-B1). In order to permit more widespread examination of the potential benefit of these intensified CHOP variants it was our objective to provide detailed information on their practicability with regard to acute haematological toxicities, adherence to the intended dosing, complications (severe infections and deaths) and required supportive care (i.e. rhG-CSF, transfusions).

Our data confirm that the CHOP-21 standard regimen is characterised by a moderate degree of haematopoietic toxicities and can be applied very closely to the intended dose and time schedule. Leucocytopenia of World Health Organization (WHO) grade 4 occurred in only 7% of all cycles in patients ≤60 years of age and in 44% of all cycles in older patients. Most therapy cycles (96%) were given without administration of rhG-CSF. Severe thrombocytopenia (WHO grade 4) and platelet transfusions were rare events (both <1% of all cycles). The time course of leucocytes and platelets during the therapy cycles showed that within 3 weeks sufficient recovery was achieved on average. Over six consecutive therapy cycles no exhaustion of the haematopoietic recovery dynamics could be noticed.

The three intensified CHOP variants were designed to achieve moderate intensification under the constraint of maintaining multicentre practicability with a conventional multicycle chemotherapy. Our data clearly show that the CHOP regimen can be given every 2 weeks for six cycles with no increased toxicity compared with the 3-weekly CHOP standard regimen. The total drug doses delivered were comparable for CHOP-14 and CHOP-21 while the total treatment duration could be shortened by 36 days in patients aged ≤60 years and by 34 days in elderly patients. Grade 4 leucocytopenia in patients aged >60 years was considerably less frequent in CHOP-14 compared with CHOP-21 treatment arms (24% versus 44%; $P < 0.001$). This effect is likely due to rhG-CSF administration. The rates of infections, the transfusion needs and the use of antibiotics were similar for both regimens. Haematopoietic recovery was possible for granulopoiesis and thrombocytopoiesis without cumulative toxicity after CHOP-14 in all age groups. We observed a slow decline in haemoglobin levels that led to a slight increase in RBC transfusions (10% versus 12% of all cycles in patients >60 years).

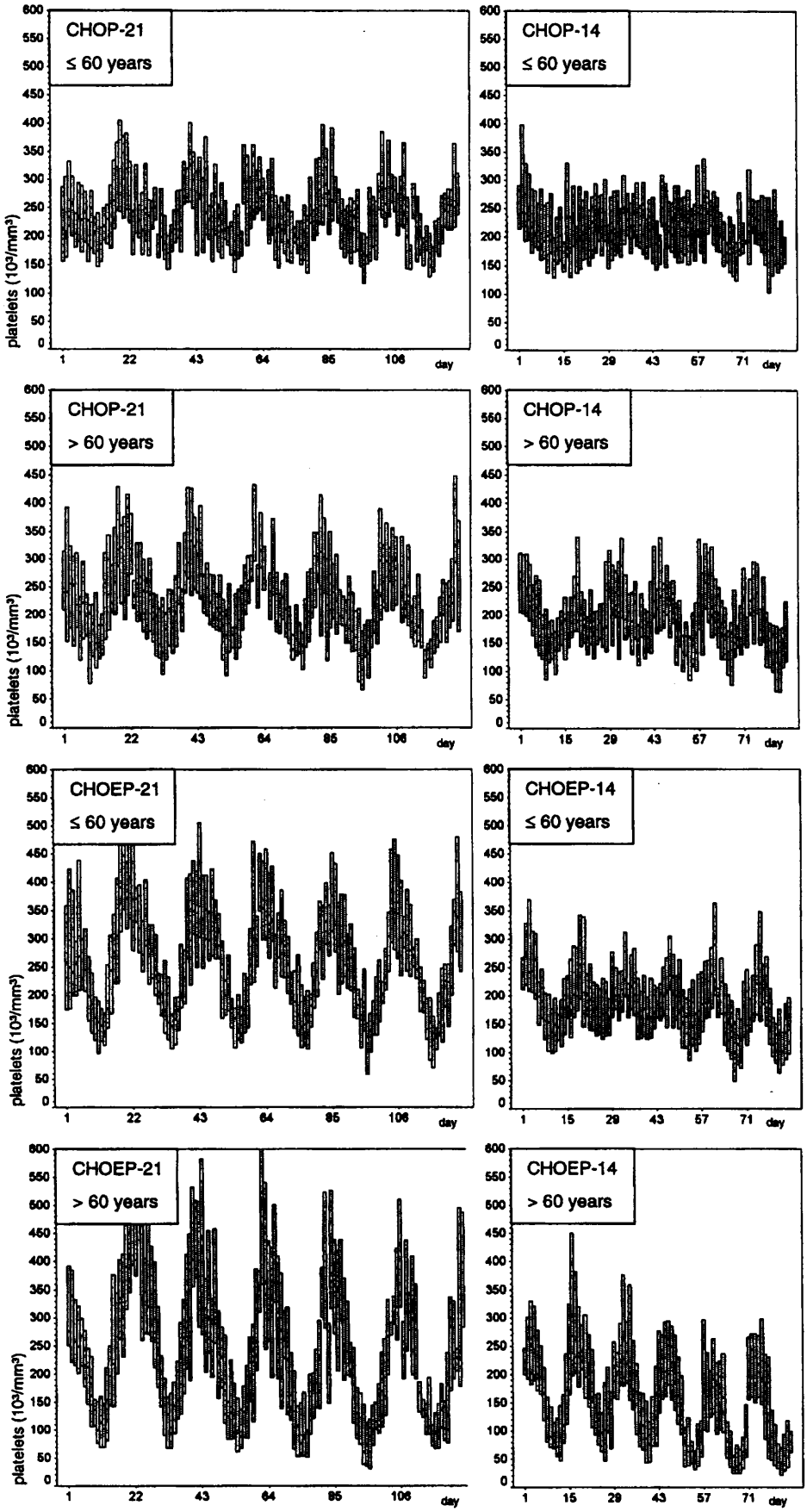
Remarkably, the mean duration of hospitalisation per cycle was 1 day shorter following CHOP-14 compared with CHOP-21 in elderly patients (4 versus 5 days; $P = 0.005$). Hence the data provide evidence that the toxicity profile of CHOP-14 (with rhG-CSF) and CHOP-21 (without rhG-CSF) is almost identical and a marked shortening of the treatment period is possible. We therefore conclude that six cycles of CHOP-14 is safe and feasible in a multicentre setting for all age groups between 18 and 75 years.

Based on the available interim analyses on treatment efficiency mentioned above the German study group decided in 2000 to consider six cycles of 2-weekly CHOP with addition of rhG-CSF as the reference treatment for its future trials in all patients aged >60 years. A trial is presently ongoing for patients aged 61–80 years comparing six versus eight cycles of CHOP-14 in a 2×2 factorial study design with or without the addition of anti-CD20 antibody (RICOVER60 trial). So far this ongoing trial supports the conclusion that CHOP-14 is a safe and feasible regimen.

As expected, the addition of etoposide to the CHOP regimen led to more haematological toxicities. Leucocytopenia, thrombocytopenia and anaemia were more pronounced in the CHOEP schemes compared with the CHOP schemes. Recovery was age dependent. In patients ≤60 years of age recovery of leucocytopenia and thrombocytopenia occurred regularly to pre-treatment levels permitting the continuation with either CHOEP-21 or CHOEP-14.

Considering also the data on the rates of infections, antibiotic use, transfusion requirements, hospitalisation and particularly fatal treatment-related toxicities, we conclude that CHOEP-21 and CHOEP-14 are feasible and safe schemes in a multicentre setting in the age group ≤60 years.

Based on the available interim analyses on treatment efficiency mentioned above, the German study group decided in 2000 to consider CHOEP as the reference treatment for its future trials in all patients aged ≤60 years. A trial is presently ongoing for these patients with low and low–intermediate International Prognostic Index comparing six cycles of CHOEP-21 with six cycles of a dose-escalated variant of CHOEP-21. Furthermore, the study group opted to use CHOEP-21 as the standard treatment in the ongoing Mabthera Intergroup trial (MINT trial) investigating the role of anti-CD20 antibodies in CHOP-like treatments in patients ≤60 years of age, a population not covered by the recent GELA trial



ts (10^3/mm^3) over the successive therapy cycles.

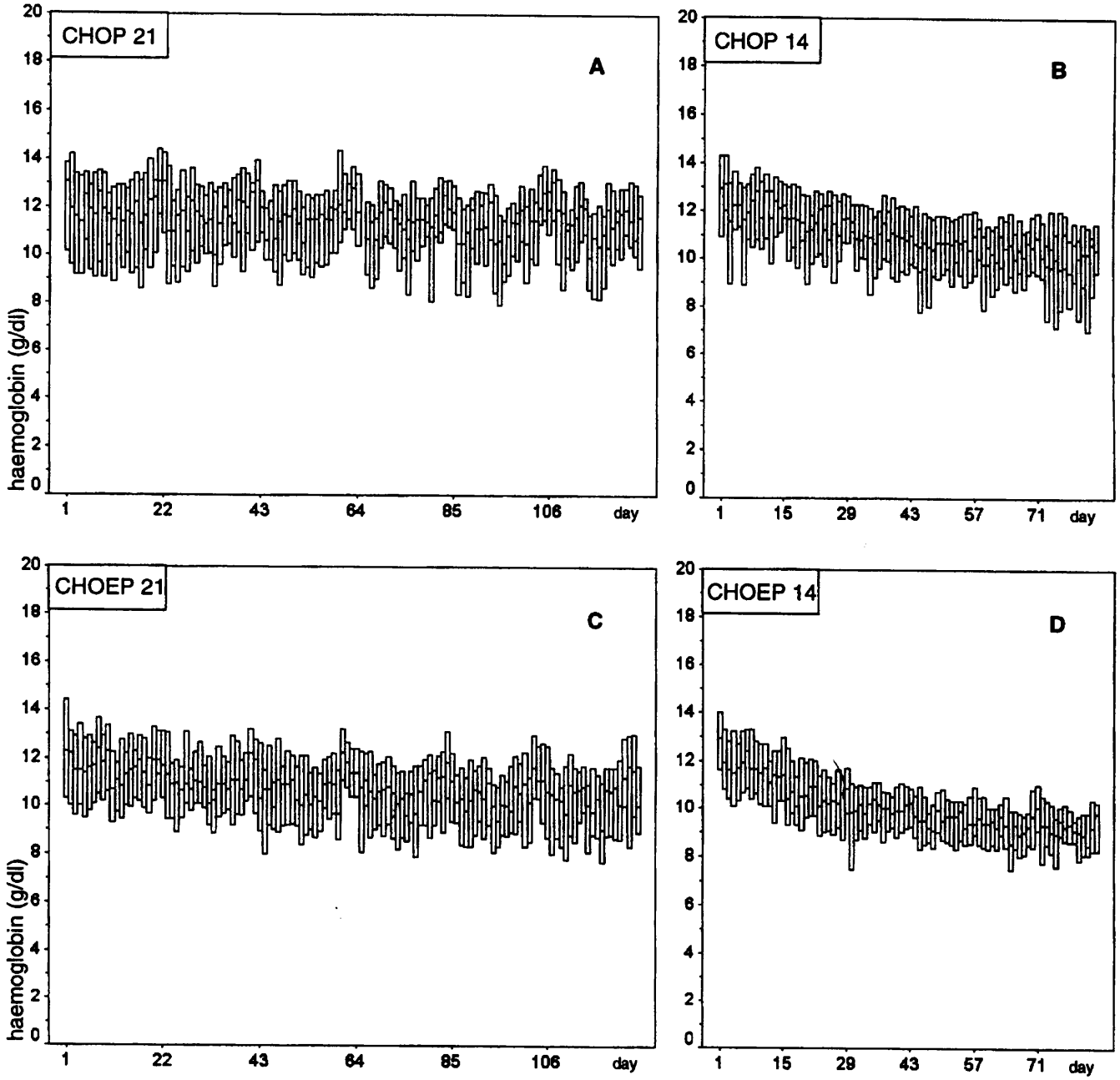


Figure 5. Haemoglobin (g/dl) over the successive therapy cycles.

[19]. So far our ongoing trials support our conclusion that CHOEP is a safe and feasible regimen in the age group <60 years.

In contrast, we recommend that the CHOEP schemes should be used with caution in patients >60 years of age. Regarding practicability we observed a substantial dose and schedule erosion, particularly for CHOEP-14. Regarding safety an increased risk of treatment-related mortality has to be taken into account.

Clearly the toxicity and feasibility data presented in this analysis have to be balanced against the treatment outcome data. The forthcoming final analysis of the NHL-B trial will provide further clarification about whether and which of the intensified CHOP regimens are superior to classical CHOP-21 with regard to tumour control and long-term outcome. Clearly large gains in outcome may encourage us to accept larger risks regarding acute toxicities and vice versa. In view of the increased aggressiveness of these schemes late sequelae such as the rate of secondary leukaemias or myelodysplastic syndromes need to be carefully monitored in the future. However, due to short follow-up the data presently available are too immature and incomplete.

An interesting observation is the large variance of WBC counts under rhG-CSF. We believe this is largely due to non-standardised intervals between rhG-CSF application and time of blood sampling. As rhG-CSF concentrations rise and fall quickly the phenomenon of bone marrow release and of demargination of leucocytes attached to the arterial walls may play a crucial role. The clinical implication is that measurements of WBC following rhG-CSF

Table 3. Toxicities and interventions (n = 5331 cycles)

	Age of patients (years)	CHOP-21 (n = 1282)	CHOP-14 (n = 1357)	CHOEP-21 (n = 1354)	CHOEP-14 (n = 1338)
Haematological toxicity (% of cycles)					
Leucocytes[a] (<1000/mm^3)	≤60	7.3	10.8	21.9	16.3
	>60	43.8	23.6	59.0	48.4
Thrombocytes[b]					
(<25000/mm^3)	≤60	0.0	0.9	1.6	3.0
	>60	0.6	2.2	5.4	17.1
(<50000/mm^3)	≤60	0.9	1.8	6.0	12.4
	>60	3.0	8.7	14.7	40.9
Haemoglobin (<8 g/dl)	≤60	1.0	1.7	2.6	8.8
	>60	4.3	7.0	9.8	19.2
Transfusion (% of cycles)					
Platelets	≤60	0.0	0.1	0.6	0.8
	>60	0.2	0.8	2.6	6.0
RBC	≤60	0.7	1.8	3.1	9.5
	>60	10.1	11.9	14.8	31.5
Non-haematological toxicity (WHO grade 3/4) (% of cycles)					
Infections	≤60	0.4	0.9	0.8	1.2
	>60	2.0	2.2	5.1	6.9
Mucositis	≤60	0.7	0.6	0.3	2.2
	>60	0.3	2.4	2.3	4.6
Neural toxicity	≤60	0.8	0.4	0.7	0.3
	>60	1.0	0.5	1.2	2.6
Antibiotics (% of cycles)	≤60	7.0	8.4	12.2	13.5
	>60	14.0	15.0	26.3	29.3
Days of hospitalisation (mean number of days per cycle)	≤60	2.7	2.8	3.9	4.1
	>60	5.4	4.3	6.5	7.1

[a]Based on the lowest documented leucocyte value. Only used if the measurement in the nadir windows is days 8–10 for 14-day regimens or days 10–12 for 21-day regimens.

[b]Based on the lowest documented thrombocyte value. Only used if the measurement in the nadir windows is days 10–12 for all regimens.

injection are somewhat invalidated and more reliable data may be obtained by measurements immediately before the daily rhG-CSF injection [20]. The time courses of WBC count under rhG-CSF observed by Crawford et al. [21] could in general be confirmed, showing a first peak on days 4 and 5 and a second peak after the nadir. We anticipate that new G-CSF molecules with a different pharmacokinetic make-up may lead to a smoothing of the variant WBC time courses [22–24].

An interesting extension of this analysis is concerned with the predictibility of haematotoxicity based on parameters available before the start of treatment. This may help to adjust individual treatment intensity in patients [25, 26]. A more detailed analysis is forthcoming.

As a consequence of the increased haematotoxicity, clearly more haematosupportive treatment (rhG-CSF and transfusions) was required during intensified CHOP variants. A median number of 10 rhG-CSF injections per cycle were given in the 2-weekly regimen. This is a considerable cost factor. At present, it is not clear whether this rhG-CSF schedule is optimal regarding cost-effectiveness. The number of G-CSF injections might be reduced without jeopardising the safety of the 2-weekly schedules. Efforts to identify rhG-CSF administration schedules that potentially are more cost-effective have been initiated using computer-based modelling of granulopoiesis [27]. In the presently ongoing RICOVER60 trial for elderly patients we use CHOP-14 with a 7-day rhG-CSF schedule from day 6 to 12.

In summary, we conclude that CHOP-14 is a safe and feasible regimen for all age groups with toxicity profiles and need for supportive treatment similar to CHOP-21 while permitting a more rapid dose delivery. CHOEP-21 and CHOEP-14 are also safe and feasible regimens for patients ≤60 years of age. CHOEP variants should be used with caution in age groups >60 years.

Table 4. Treatment-related mortality and second cancers ($n = 959$ patients)

	Age of patients (years)	CHOP-21 ($n = 232$)	CHOP-14 ($n = 238$)	CHOEP-21 ($n = 244$)	CHOEP-14 ($n = 245$)
Treatment-related mortality during treatment (no. of patients)					
	≤60	0	0	1	2
	>60	3	6	7	11
Cycle 1		2	1	4	6
Cycles 2–6		1	5	4	7
Second cancers (no. of patients)					
ALL/MDS/AML	≤60	0	2	1	2
	>60	0	0	0	0
Solid tumour	≤60	0	2	0	0
	>60	2	2	3	0

ALL, acute lymphoblastic leukaemia; AML, acute myelogenous leukaemia; MDS, myelodysplastic syndrome.

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