Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60)

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Summary

Background Cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) is used to treat patients with non-Hodgkin lymphoma. Interval decrease from 3 weeks of treatment (CHOP-21) to 2 weeks (CHOP-14), and addition of rituximab to CHOP-21 (R-CHOP-21) has been shown to improve outcome in elderly patients with diffuse large B-cell lymphoma (DLBCL). This randomised trial assessed whether six or eight cycles of R-CHOP-14 can improve outcome of these patients compared with six or eight cycles of CHOP-14.

Methods 1222 elderly patients (aged 61–80 years) were randomly assigned to six or eight cycles of CHOP-14 with or without rituximab. Radiotherapy was planned to sites of initial bulky disease with or without extranodal involvement. The primary endpoint was event-free survival; secondary endpoints were response, progression during treatment, progression-free survival, overall survival, and frequency of toxic effects. Analyses were done by intention to treat. The trial is registered on National Cancer Institute website, number NCT00052936 and as EU-20243.

Findings 3-year event-free survival was 47·2% after six cycles of CHOP-14 (95% CI 41·2–53·3), 53·0% (47·0–59·1) after eight cycles of CHOP-14, 66·5% (60·9–72·0) after six cycles of R-CHOP-14, and 63·1% (57·4–68·8) after eight cycles of R-CHOP-14. Compared with six cycles of CHOP-14, the improvement in 3-year event-free survival was 5·8% (–2·8–14·4) for eight cycles of CHOP-14, 19·3% (11·1–27·5) for six cycles of R-CHOP-14, and 15·9% (7·6–24·2) for eight cycles of R-CHOP-14. 3-year overall survival was 67·7% (62·0–73·5) for six cycles of CHOP-14, 66·0% (60·1–71·9) for eight cycles of CHOP-14, 78·1% (73·2–83·0) for six cycles of R-CHOP-14, and 72·5% (67·1–77·9) for eight cycles of R-CHOP-14. Compared with treatment with six cycles of CHOP-14, overall survival improved by –1·7% (–10·0–6·6) after eight cycles of CHOP-14, 10·4% (2·8–18·0) after six cycles of R-CHOP-14, and 4·8% (–3·1–12·7) after eight cycles of R-CHOP-14. In a multivariate analysis that used six cycles of CHOP-14 without rituximab as the reference, and adjusting for known prognostic factors, all three intensified regimens improved 3-year event-free survival (eight cycles of CHOP-14: RR [relative risk] 0·76 [0·60–0·95], p=0·0172; six cycles of R-CHOP-14: RR 0·51 [0·40–0·65], p<0·0001; eight cycles of R-CHOP-14: RR 0·54 [0·43–0·69], p<0·0001). Progression-free survival improved after six cycles of R-CHOP-14 (RR 0·50 [0·38–0·67], p<0·0001), and eight cycles of R-CHOP-14 (RR 0·59 [0·45–0·77], p=0·0001). Overall survival improved only after six cycles of R-CHOP-14 (RR 0·63 [0·46–0·85], p=0·0031). In patients with a partial response after four cycles of chemotherapy, eight cycles were not better than six cycles.

Interpretation Six cycles of R-CHOP-14 significantly improved event-free, progression-free, and overall survival over six cycles of CHOP-14 treatment. Response-adapted addition of chemotherapy beyond six cycles, though widely practiced, is not justified. Of the four regimens assessed in this study, six cycles of R-CHOP-14 is the preferred treatment for elderly patients, with which other approaches should be compared.

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Introduction

For more than 25 years, the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen[1] has been standard care for aggressive lymphomas.[2] The French Groupe de l'Etude des Lymphomes de l'Adulte (GELA) added the monoclonal anti-CD20 antibody rituximab to eight cycles of CHOP (CHOP-21),[3] whereas the German High-Grade Non-Hodgkin Lymphoma Study Group (Deutsche Studiengruppe Hochmaligne Lymphome; DSHNHL) shortened intervals between six cycles of treatment with CHOP from 3 weeks to 2 weeks (CHOP-14).[4] Both approaches have been shown to improve the outcome of elderly patients, notably without relevant additional toxicity. To compare six cycles with eight cycles of chemotherapy and to address the question whether further improvement could be achieved by adding rituximab to the dose-dense CHOP-14 regimen, the DSHNHL designed the rituximab with CHOP over age 60 years (RICOVER-60) trial, in which elderly patients with diffuse large B-cell lymphoma (DLBCL) were randomly assigned to receive six or eight cycles of chemotherapy, both with and without eight cycles of rituximab. The number of rituximab cycles was kept constant in both R-CHOP-14 arms because we

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intended to compare the numbers of chemotherapy cycles without the confounder of differing rituximab regimens.

Methods

Patients

Patients were eligible if they had previously untreated, biopsy-confirmed aggressive non-Hodgkin lymphoma of the B-cell type according to the Revised European–American Lymphoma Classification[5] (translated into the WHO classification[6]) and were aged between 61 years and 80 years. Histological diagnosis was reviewed centrally by a panel of five expert haematopathologists. Patients with previous lymphoma associated with acquired immunodeficiency syndrome, diagnosis or history of indolent lymphoma or other malignancies, marked impairment of cardiac, pulmonary, hepatic, or renal function, WHO performance status over 2, initial white-blood count (WBC) under $2 \cdot 5 \times 10^3$/L, initial platelet count under 100×10^3/L, or inability to comply with study requirements were excluded. Patients had mandatory baseline assessments including clinical assessment, relevant laboratory tests (ie, haemoglobin, platelets, total WBC count, differential WBC count, serum protein, albumin, serum creatinine, urea, uric acid, calcium, potassium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, lactate dehydrogenase, β2 microglobulin, and urinalysis), chest and abdomen CT scans, and bone-marrow biopsy. The study was undertaken in accordance with the Helsinki declaration. The protocol was approved by the ethical review committee of each participating centre. All patients gave written informed consent.

Treatment

A pre-phase treatment (single intravenous injection of 1 mg vincristine and 100 mg prednisone orally for 7 days) was mandatory to improve the performance status of patients and to ameliorate side-effects of the first chemotherapy cycle. For patients who complained of fatigue after tapering the prednisone, hydrocortisone (20 mg orally in the morning and 10 mg orally at 1200 h) was recommended. The CHOP regimen[1] consisted of cyclophosphamide (750 mg/m² intravenously), doxorubicin (50 mg/m² intravenously), vincristine (2 mg intravenously) on day 1 and prednisone (100 mg orally) on days 1–5. CHOP-14 was repeated every 2 weeks. All patients received recombinant human granulocyte-colony stimulating factor (G-CSF; ie, filgrastim or lenograstim) starting on day 6 until recovery of leucocytes. After analysis of the first 500 patients showed a significant increase in severe infections, the recommendation was to give G-CSF starting on day 4, which was not followed by all participating institutions. The next chemotherapy cycle was scheduled for day 15, after recovery of WBC ($>2 \cdot 5 \times 10^9$/L) and platelets ($>80 \times 10^9$/L). Patients were randomly assigned to receive six or eight cycles of chemotherapy with or without 8 bi-weekly dosing of rituximab (375 mg/m²). Patients with initial bulky disease (defined as lymphoma masses or conglomerates with a diameter ≥7·5 cm) or extranodal involvement received radiotherapy (36 Gy) to these areas irrespective of the result of chemotherapy.

All patients underwent restaging after four cycles of treatment and after the end of treatment. Follow-up assessments were done every 3 months during the first 2 years, and every 6 months during the third to fifth year by use of physical examination, relevant laboratory tests (the same as those done for staging) and CT of the chest and abdomen. Response was assessed by the treating physician and classified as complete response, unconfirmed complete response, partial response, stable disease, or progressive disease according to the International Workshop criteria.[7] Adverse events reported by the patient or noted by the treating physician were coded on case-report forms according to National Cancer Institute Common Toxicity Criteria (NCI-CTC version 2.0) grades. An adverse event was defined as any adverse change from the patient's baseline condition after the start of treatment, whether or not it was deemed to be associated with treatment. WHO grades for haematotoxicity were assessed from blood counts within treatment-specific nadir windows. Drugs used in this trial are listed in the webpanel.

Statistical analysis

Randomisation was undertaken at a 1:1:1:1 ratio by use of the Pocock minimisation algorithm after stratification for centres, increased lactate dehydrogenase, advanced stage (ie, stage III or IV), performance status (Eastern Cooperative Oncology Group [ECOG] 0 or 1 *vs* ECOG 2 or 3), extranodal sites, age over 70 years, and presence of bulky disease. To ensure balanced randomisations at any time, patients were randomised centrally by a data manager at the study centre (Homburg, Germany) by use of a computer program with an algorithm that accounted for randomisations that had occurred previously; no blocks were used. The trial was planned in a 2×2 factorial design that compared patients randomly assigned to receive six cycles with those assigned eight cycles of chemotherapy, and that compared patients randomly assigned to rituximab with those who were not. The trial was powered to show a hazard ratio (HR) of 0·749 or an improvement of 10% in the primary endpoint of 3-year event-free survival, and had a power of 80% and a significance level of 5% in a two-sided logrank test for each of the two contrasts, requiring 800 patients including dropouts (software for sample size calculations: nQuery Advisor 6.0). To account for an interaction term (ie, differential effect of the addition of rituximab in treatment cycles of six and eight and vice versa) 988 patients were necessary to detect a 9% difference in 3-year event-free survival with a power of 80% and a significance level of 5% in a two-sided logrank test. To enable an additional analysis with a power of 80% of only those patients who were treated according to the protocol, a minimum of

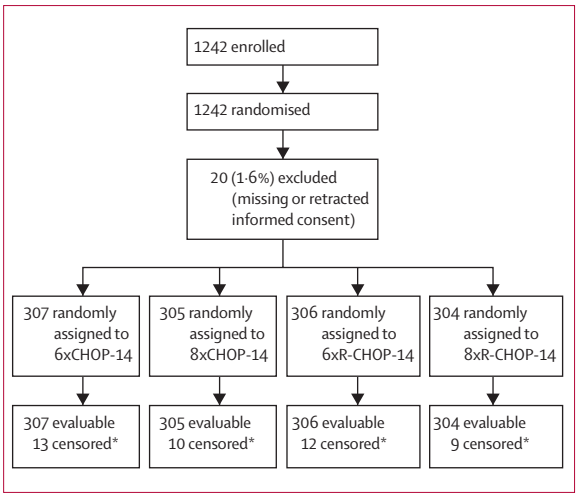


Figure 1: **Trial profile**
*On June 14, 2005, when the trial was stopped.

1098 patients were necessary. Proportional hazard models were used for event-free, progression-free, and overall survival. Logistic regression was used for secondary binary endpoints (ie, proportions of patients with remissions and progressions). In all models, we adjusted for the stratification variables. Analysis of all endpoints was done by intention to treat.

The primary endpoint was event-free survival (defined as time from randomisation to disease progression, start of salvage treatment, additional (unplanned) treatments, relapse, or death from any cause); secondary endpoints were response, progression during treatment, frequency of toxic effects, progression-free survival (defined as time from randomisation to progression, relapse, or death from any cause), and overall survival (defined as time from randomisation to death from any cause), and were analysed by use of the Kaplan-Meier method. These endpoints are given at 3 years with 95% CI.

A first planned interim analysis of 402 patients on May 19, 2003, showed that none of the stopping rules were fulfilled. The second planned interim analysis was done on May 27, 2005. At that time point, 828 patients with CD20+ aggressive B-cell lymphoma were evaluable. There was no interaction and the 2×2 factorial analysis showed an improved event-free survival after R-CHOP-14 treatment ($p<0·0001$). Since the empirical p value of the logrank test statistics for event-free survival was below the critical value for the interim analysis ($p_{crit}=0·0163$), the formal criterion for stopping the trial according to the alpha spending function[8] was met and the trial was stopped on June 14, 2005. 44 of 1222 patients who were still under treatment at that time were censored on that date. For the final analysis, a multivariate test showed a relevant interaction term (relative risk [RR] 1·39 [95% CI 0·98–1·98], p=0·0677; proportional hazard model for event-free survival) that required modelling the effect of each of the three intensified regimens (eight cycles of

	6xCHOP-14 (n=307)	8xCHOP-14 (n=305)	6xR-CHOP-14 (n=306)	8xR-CHOP-14 (n=304)
Sex, n (%)				
Men	170 (55)	155 (51)	168 (55)	157 (52)
Women	137 (45)	150 (49)	138 (45)	147 (48)
Age, years				
Median (range)	68 (61–80)	68 (61–80)	69 (61–80)	68 (61–80)
61–65, n (%)	90 (29)	115 (38)	90 (29)	108 (36)
66–70, n (%)	107 (35)	80 (26)	103 (34)	85 (28)
71–75, n (%)	71 (23)	70 (23)	73 (24)	71 (23)
76–80, n (%)	39 (13)	40 (13)	40 (13)	40 (13)
LDH >UNV, n (%)	153 (50)	148 (49)	152 (50)	151 (50)
ECOG >1, n (%)	42 (14)	45 (15)	43 (14)	46 (15)
Stage, n (%)				
III or IV	154 (50)	158 (52)	152 (50)	155 (51)
I	70 (23)	72 (24)	68 (22)	58 (19)
II	83 (27)	75 (25)	86 (28)	91 (30)
III	78 (25)	81 (27)	85 (28)	72 (24)
IV	76 (25)	77 (25)	67 (22)	83 (27)
Extranodal sites >1	50 (16)	57 (19)	52 (17)	57 (19)
IPI				
1	98 (32)	90 (30)	94 (31)	90 (30)
2	80 (26)	87 (29)	89 (29)	83 (27)
3	80 (26)	78 (26)	78 (25)	77 (25)
4 or 5	49 (16)	50 (16)	45 (15)	54 (18)
Bulky disease, n	116 (38)	114 (37)	117 (38)	116 (38)
B symptoms, n	109 (36)	93 (30)	98 (32)	99 (33)
BM involvement, n	20 (7)	15 (5)	14 (5)	24 (8)
Radiotherapy assigned, n	158 (51)	173 (57)	167 (55)	158 (52)
Reference pathology available, n (%)	298 (97)	300 (98)	297 (97)	296 (97)
B cell				
DLBCL	235 (79)	240 (80)	237 (80)	237 (80)
Centroblastic	137 (46)	126 (42)	128 (43)	125 (42)
Immunoblastic	19 (6)	17 (6)	12 (4)	15 (5)
Plasmoblastic	..	..	3 (1)	4 (1)
Anaplastic large cell	4 (1)	2 (0·7)	8 (3)	5 (2)
T-cell-rich	8 (3)	5 (2)	3 (1)	2 (0·7)
NOS	64 (21)	83 (28)	80 (27)	86 (29)
PMBCL	3 (1)	7 (2)	3 (1)	..
Follicular grade III	19 (6)	14 (5)	12 (4)	16 (5)
Follicular grade III + DLBCL	14 (5)	18 (6)	9 (3)	14 (5)
Lymphoblastic	..	..	1 (0·3)	..
Burkitt's lymphoma	..	3 (1)	2 (0·7)	4 (1)
Burkitt–like	2 (0·7)	3 (1)	1 (0·3)	2 (0·7)
Mantle-cell blastic	3 (1)	3 (1)	6 (2)	5 (2)
Mantle-cell classical	..	..	1 (0·3)	1 (0·3)
Aggressive marginal	3 (1)	2 (0·7)	5 (2)	3 (1)
NOS	7 (2)	7 (2)	7 (2)	4 (1)
Unclassified (technically insufficient)	4 (1)	5 (2)	7 (2)	6 (2)
Other lymphoma or no lymphoma	11 (4)	5 (2)	9 (3)	4 (1)

LDH=lactate dehydrogenase. UNV=upper normal value. ECOG=Eastern Cooperative Oncology Group performance status. IPI=International Prognostic Index. BM=bone marrow. DLBCL=diffuse large B-cell lymphoma. NOS=not otherwise specified. PMBCL=primary mediastinal B-cell lymphoma.

Table 1: **Characteristics of patients**

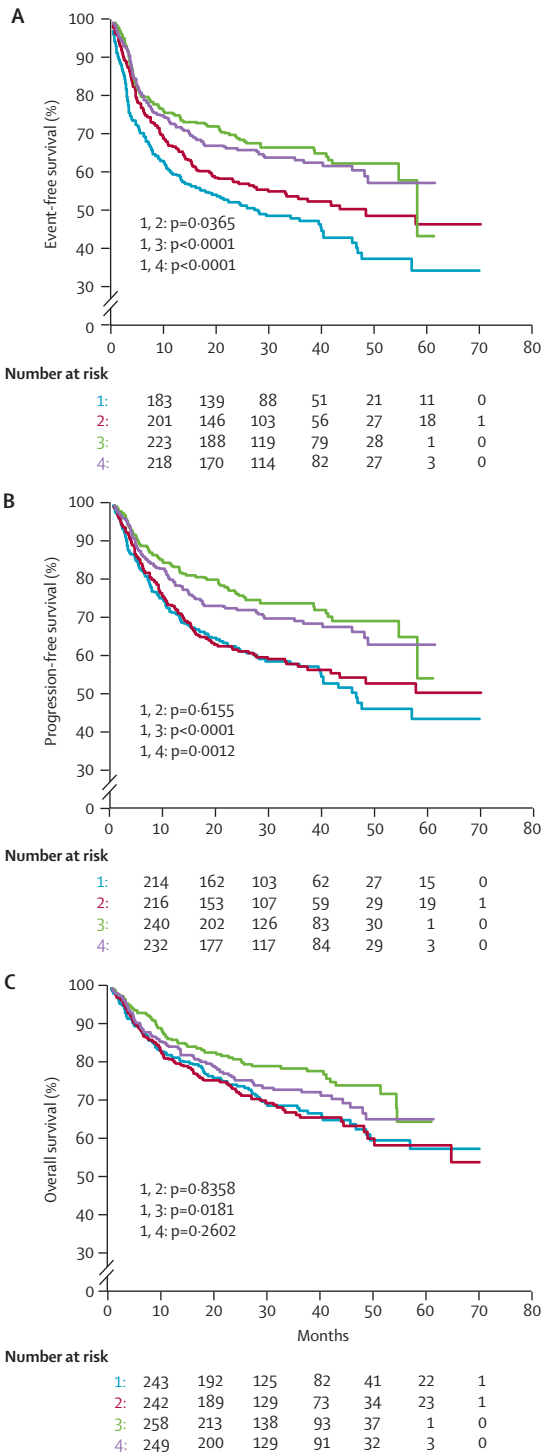


***Figure 2*: Event-free (A), progression-free (B), and overall (C) survival of 1222 elderly patients with aggressive CD20+ B-cell lymphoma treated in the RICOVER-60 trial**

Patients were assigned to six or eight cycles of CHOP-14 with or without eight cycles of rituximab. 1=6×CHOP-14; 2=8×CHOP-14; 3=6×R-CHOP-14; 4=8×R-CHOP-14.

	6xCHOP-14 (n=307)	8xCHOP-14 (n=305)	6xR-CHOP-14 (n=306)	8xR-CHOP-14 (n=304)
Complete response, n (%); 95% CI	209 (68); 63–73	219 (72); 66–77	238 (78); 73–82	230 (76); 70–80
p	..	p=0·3150	p=0·0069	p=0·0372
Complete response after additional therapy, n (%); 95% CI	2 (0·7); 0·1–2·3	3 (1); 0·2–2·9	5 (2); 0·5–3·8	5 (2); 0·5–3·8
p	..	p=0·6854	p=0·2858	p=0·2842
Partial response, n (%); 95% CI	20 (7); 4–10	13 (4); 2–7	11 (4); 2–6	8 (3); 1–5
p	..	p=0·2174	p=0·0990	p=0·0217
Stable disease, n (%); 95% CI	2 (0·7); 0·1–2·3	2 (0·7); 0·1–2·4	0; 0–1	4 (1); 0·4–3·3
p	..	p=1·0000	p=0·4992	p=0·4489
Progressive disease, n (%); 95% CI	25 (8); 5–12	29 (10); 7–13	20 (7); 4–10	19 (6); 4–10
p	..	p=0·5517	p=0·4455	p=0·3654
Treatment-associated deaths, n (%); 95% CI	25 (8); 5–12	25 (8); 5–12	17 (6); 3–9	25 (8); 5–12
p	..	p=0·9808	p=0·2048	p=0·9711
Unknown, n (%); 95% CI	24 (8); 5–11	14 (5); 3–8	15 (5); 3–8	13 (4); 2–7
p	..	p=0·0981	p=0·1392	p=0·0665
3-year EFS; 95% CI	47·2%; 41·2–53·3	53·0%; 47·0–59·1	66·5%; 60·9–72·0	63·1%; 57·4–68·8
p	..	p=0·0365	p<0·0001	p<0·0001
3-year PFS, 95% CI	56·9%; 50·8–63·0	56·9%; 50·8–63·0	73·4%; 68·1–78·7	68·8%; 63·2–74·5
p	..	p=0·6155	p<0·0001	p=0·0012
3-year OS, 95% CI	67·7%; 62·0–73·5)	66·0%; 60·1–71·9	78·1%; 73·2–83·0	72·5%; 67·1–77·9
p	..	p=0·8358	p=0·0181	p=0·2602

EFS=event-free survival. PFS=progression-free survival. OS=overall surival. p values were derived from comparisons with 6xCHOP-14 treatment.

***Table 2*: Treatment findings**

CHOP-14, six cycles of R-CHOP-14, and eight cycles of R-CHOP-14) by use of three indicator variables in all multivariate models. All tests for significance were two-sided and were adjusted for multiple comparisons of treatment regimens. Characteristics of patients, toxic effects according to the NCI-CTC criteria (version 2), therapeutic interventions and responses between treatment regimens were compared by χ^2 tests and, if necessary, by Fisher's exact tests. Dose reductions, treatment duration for patients with at least two courses chemotherapy and relative dose intensity were assessed according to Kaplan-Meier as described elsewhere.[9] Statistical analyses were done with SPSS (version 11.5). The trial is registered on the National Cancer Institute website, number NCT00052936 and as EU-20243.

	EFS			PFS			Death		
	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p
8xCHOP-14	0·76	0·60–0·95	0·0172*	0·92	0·72–1·18	0·4906*	0·98	0·74–1·30	0·8969*
6xR-CHOP-14	0·51	0·40–0·65	<0·0001*	0·50	0·38–0·67	<0·0001*	0·63	0·46–0·85	0·0031*
8xR-CHOP-14	0·54	0·43–0·69	<0·0001*	0·59	0·45–0·77	0·0001*	0·78	0·58–1·05	0·1015*
LDH >UNV	1·53	1·26–1·86	<0·0001	1·75	1·41–2·17	<0·0001	1·77	1·39–2·27	<0·0001
ECOG >1	1·70	1·36–2·13	<0·0001	1·59	1·24–2·03	0·0002	1·67	1·29–2·16	<0·0001
Extranodal involvement >1	1·27	1·01–1·59	0·0402	1·45	1·14–1·85	0·0024	1·44	1·10–1·87	0·0074
Stage III or IV	1·57	1·28–1·93	<0·0001	1·76	1·39–2·22	<0·0001	1·59	1·23–2·06	0·0004
Bulky disease	0·96	0·80–1·16	0·7032	0·91	0·74–1·12	0·3526	1·14	0·91–1·43	0·2616
Age >70 years	1·34	1·12–1·60	0·0014	1·43	1·17–1·73	0·0004	1·77	1·43–2·20	<0·0001

EFS=event-free survival. PFS=progression-free survival. *p value derived from comparison with 6xCHOP-14 treatment.

Table 3: **Multivariate analysis of outcome adjusted for strata**

Role of the funding source

The study was funded by Deutsche Krebshilfe (German Cancer Aid), an independent charity. The funding source had no role in the design, data collection, data analysis, or interpretation of the findings. MP, JS, MZ, RS, and ML had full access to the raw data. All authors had final responsibility to submit for publication.

Results

Between July 1, 2000, and June 14, 2005, 1242 patients were enrolled in 203 institutions in Germany, Czech Republic, and Switzerland. 20 patients were excluded because of missing or retracted informed consent, leaving 1222 for the intention-to-treat analysis (figure 1). There were no significant differences in numbers of excluded patients between treatment regimens. Of the 1222 eligible patients, 307 patients were randomly assigned to receive six cycles of CHOP-14, 305 patients to eight cycles of CHOP-14, 306 patients to six cycles of R-CHOP-14, and 304 patients to eight cycles of R-CHOP-14. 656 (54%) patients were assigned to radiotherapy to areas of primary bulky disease (ie, tumour size ≥7·5 cm) or extranodal disease. Radiotherapy according to protocol was given to 417 (34%) patients. There were no significant differences in radiotherapy use between treatment regimens (table 1). Six patients (one assigned six cycles of CHOP-14; one assigned eight cycles of CHOP-14; two assigned six cycles of R-CHOP-14; and two assigned eight cycles of R-CHOP-14) received radiotherapy not planned according to protocol. Clinical presentation and risk factors were well-balanced between treatment groups (table 1).

Median length of observation from the day of randomisation was 34·5 months (range 0·2–70·1). For the univariate analysis, figure 2 shows curves for event-free survival, progression-free survival, and overall survival, and also logrank tests. Table 2 shows these endpoints at 3 years. 3-year event-free survival was 47·2% after six cycles of CHOP-14 (95% CI 41·2–53·3), 53·0% after eight cycles of CHOP-14 (47·0–59·1), 66·5% after six cycles of R-CHOP-14 (60·9–72·0), and 63·1% after eight cycles of R-CHOP-14 (57·4–68·8). Compared with treatment with six cycles of CHOP-14, event-free survival improved by 5·8% (–2·8–14·4) after eight cycles of CHOP-14, 19·3% (11·1–27·5) after six cycles of R-CHOP-14, and 15·9% (7·6–24·2) after eight cycles of R-CHOP-14. 3-year progression-free survival was 56·9% (50·8–63·0) after six cycles of CHOP-14, 56·9% (50·8–63·0) after eight cycles of CHOP-14, 73·4% (68·1–78·7) after six cycles of R-CHOP-14, and 68·8% (63·2–74·5) after eight cycles of R-CHOP-14. Compared with treatment with six cycles of CHOP-14, 3-year progression-free survival improved by 0% (–8·6–8·6) after eight cycles of CHOP-14, 16·5% (8·4–24·6) after six cycles of R-CHOP-14, and 11·9% (3·6–20·2) after eight cycles of R-CHOP-14. 3-year overall survival was 67·7% (62·0–73·5) after six cycles of CHOP-14, 66·0% (60·1–71·9) after eight cycles of CHOP-14, 78·1% (73·2–83·0) after six cycles of R-CHOP-14, and 72·5% (67·1–77·9) after eight cycles of R-CHOP-14. Compared with treatment with six cycles of CHOP-14, 3-year overall survival improved by –1·7% (–10·0–6·6) after eight cycles of CHOP-14, 10·4% (2·8–18·0) after six cycles of R-CHOP-14, and 4·8% (–3·1–12·7) after eight cycles of R-CHOP-14.

In a multivariate Cox proportional hazard model that was adjusted for stratification variables by use of six cycles of CHOP-14 without rituximab as the reference (table 3), all three intensified regimens improved event-free survival. Progression-free survival improved after six cycles of R-CHOP-14 and eight cycles of R-CHOP-14, but overall survival improved only after six cycles of R-CHOP-14 treatment.

The proportion of patients with complete remission ranged between 68% of those assigned six cycles of CHOP-14 and 78% of those assigned six cycles of R-CHOP-14 treatment. Compared with six cycles of CHOP-14 (68% [95% CI 63–73]), the proportion of

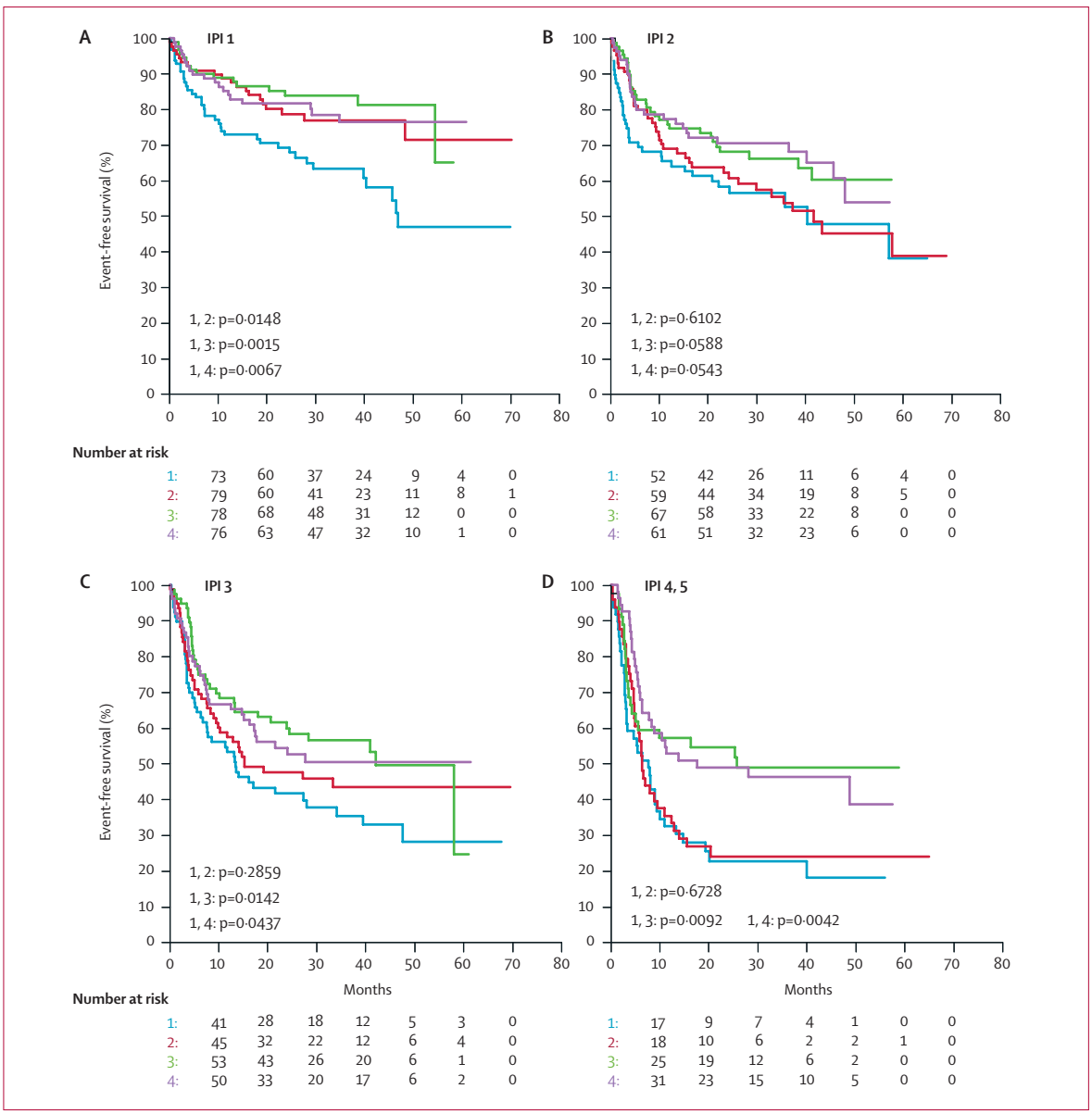
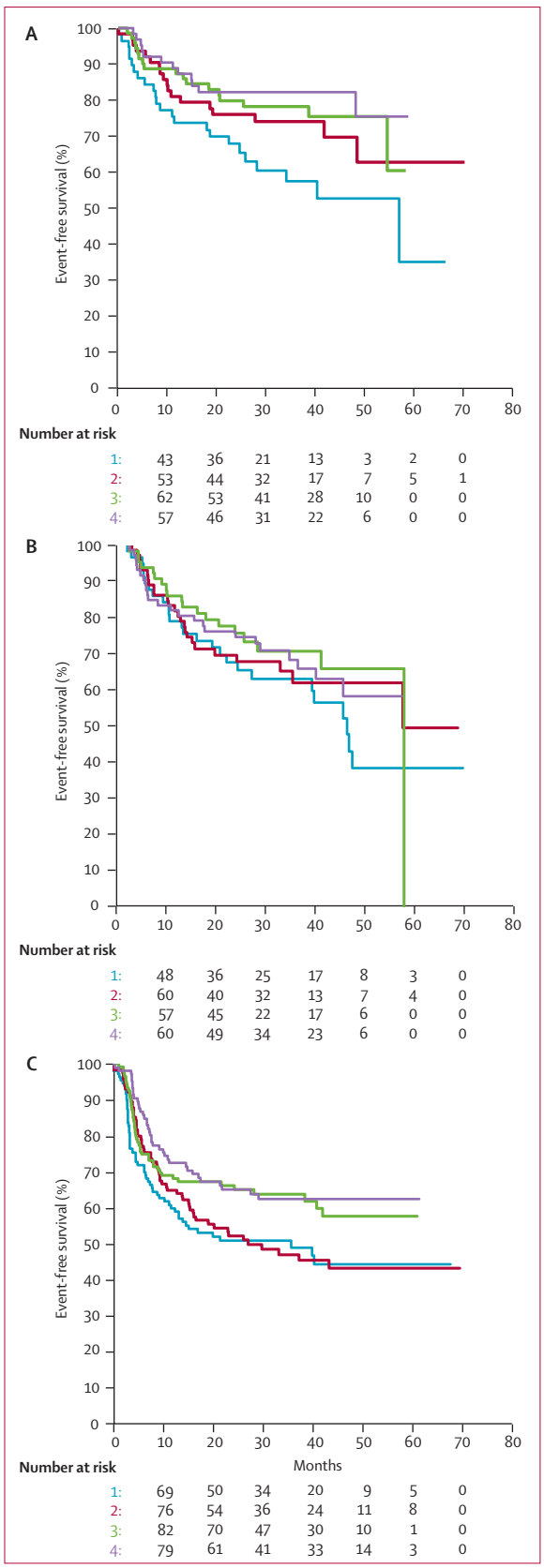


***Figure 3*: Event-free survival of elderly patients according to International Prognostic Index (IPI) risk group**
(A) Low-risk patients (6×CHOP-14: n=98; 8×CHOP-14: n=90; 6×R-CHOP-14: n=94; 8×R-CHOP-14: n=90;). (B) Low-intermediate risk patients (6×CHOP-14: n=80; 8×CHOP-14: n=87; 6×R-CHOP-14: n=89; 8×R-CHOP-14: n=83;). (C) High-intermediate risk patients (6×CHOP-14: n=80; 8×CHOP-14: n=78; 6×R-CHOP-14: n=78; 8×R-CHOP-14: n=77). (D) High-risk patients (6×CHOP-14: n=49; 8×CHOP-14: n=50; 6×R-CHOP-14: n=45; 8×R-CHOP-14: n=54). 1=6×CHOP-14. 2=8×CHOP-14. 3=6×R-CHOP-14. 4=8×R-CHOP-14.

complete remissions was significantly higher after six cycles of R-CHOP-14 (78% [73–82], p=0·0069), significantly higher after eight cycles of R-CHOP-14 (76% [70–80]) only if not corrected for multiple testing (p=0·0372, which is >0·0167 [or >0·05:3], the crucial p value after Bonferroni correction for multiple testing), and not higher after eight cycles of CHOP-14 (72% [66–77], p=0·3150).

Cox modelling was undertaken to assess the decrease in relative risk of each of the treatments for event-free survival, progression-free survival, and overall survival (table 3). Six cycles of CHOP-14 were used as the reference. Adjustments were made for increased lactose dehydrogenase, disease stage III or IV, ECOG performance status greater than 1, involvement of more than one extranodal site, presence of bulky disease, and age over 70 years. Whereas all International Prognostic Index (IPI) parameters were prognostic for event-free survival, progression-free survival, and overall survival, bulky disease (ie, tumour size ≥7·5 cm) was not an adverse prognostic factor for any of these endpoints.



A planned exploratory subgroup analysis of the four risk groups according to the IPI[12] showed a benefit of the addition of rituximab for each of these subgroups in terms of event-free survival. In the low-risk group (figure 3), all three intensified treatment regimens had significantly better event-free survival compared with six cycles of CHOP-14 (eight cycles of CHOP-14: p=0·0148; six cycles of R-CHOP-14: p=0·0015; eight cycles of R-CHOP-14: p=0·0067). Compared with six cycles of CHOP-14, both rituximab-containing treatment regimens were not significantly better (six cycles of R-CHOP-14: p=0·0588; eight cycles of R-CHOP-14: p=0·0543) in the low-intermediate risk group, whereas in the intermediate-high risk group and high-risk groups, both rituximab-containing treatment regimens had a significantly better event-free survival (high-intermediate risk: six cycles of R-CHOP-14: p=0·0142; eight cycles of R-CHOP-14: p=0·0437; high risk: six cycles of R-CHOP-14: p=0·0092, eight cycles of R-CHOP-14: p=0·0042). There was no difference in event-free survival between the rituximab groups when patients assigned to radiotherapy (six cycles of R-CHOP-14: n=167; eight cycles of R-CHOP: n=158; logrank p=0·7084) or no radiotherapy (six cycles of R-CHOP-14: n=139; eight cycles of R-CHOP-14: n=146; logrank p=0·6766) were compared, showing that the similar efficacy between six cycles of R-CHOP-14 and eight cycles of R-CHOP-14 was not due to radiotherapy use.

Furthermore, eight cycles of R-CHOP-14 was not better than six cycles in patients with complete response, unconfirmed complete response, or partial response at interim restaging after four cycles (figure 4). There was also no difference in event-free survival between six cycles of R-CHOP-14 and eight cycles of R-CHOP-14 when patients with partial responses at mid-treatment who were assigned to radiotherapy (six cycles of R-CHOP-14: n=85; eight cycles of R-CHOP-14: n=70; logrank p=0·4541) or no radiotherapy (six cycles of R-CHOP-14: n=37; eight cycles of R-CHOP-14: n=37; logrank p=0·9713) were compared.

Additional sensitivity analyses of the primary and secondary endpoints restricted to 949 patients with DLBCL yielded findings almost identical with the entire population (data not shown). The same occurred when the analysis was restricted to patients with pathological reviews confirming the diagnosis of CD20+ aggressive lymphoma, 1123 patients who did not have any exclusion criteria, 1074 patients who completed treatment without any protocol violation, and when the 44 censored patients still under treatment when the trial was stopped were included in the analysis (data not shown). Furthermore, patients with stage I disease without bulky disease had

***Figure 4*: Event-free survival of patients**
Patients with complete responses (A), unconfirmed complete responses (B), and partial response (C) after four cycles of CHOP-14 with and without rituximab. 1=6×CHOP-14; 2=8×CHOP-14; 3=6×R-CHOP-14; 4=8×R-CHOP-14. Complete responses (n=261), unconfirmed complete responses (n=276), partial response (n=459).

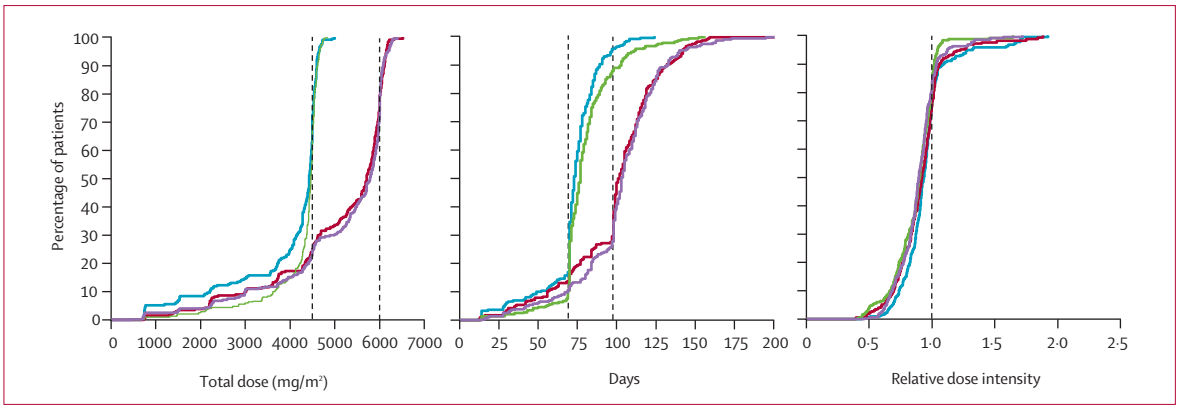


***Figure 5*: Total doses of cyclophosphamide, adherence to 14-day schedule, and relative dose intensities of cyclophosphamide in the RICOVER-60 trial**
Blue line=6×CHOP-14. Red line=8×CHOP-14. Green line=6×R-CHOP-14. Purple line=8×R-CHOP-14.

	6xCHOP-14 (n=307)	8xCHOP-14 (n=305)	6xR-CHOP-14 (n=306)	8xR-CHOP-14 (n=304)	p
Leucocytopenia*	93/193 (48)	93/195 (48)	103/197 (52)	108/218 (50)	0·8017
Thrombocytopenia	18/187 (10)	34/198 (17)	23/192 (12)	33/212 (16)	0·1242
Anaemia	46/284 (16)	66/287 (23)	45/283 (16)	77/283 (27)	0·0013
Arrhythmia	13/280 (5)	8/281 (3)	11/281 (4)	18/287 (6)	0·2437
Cardiac function	5/277 (2)	5/281 (2)	7/279 (3)	8/284 (3)	0·7917
Neuropathy	20/279 (7)	30/284 (11)	20/284 (7)	24/290 (8)	0·3946
Mucositis	8/281 (3)	18/283 (6)	15/282 (5)	25/288 (9)	0·0278
Infection	83/284 (29)	88/286 (31)	79/287 (28)	101/291 (35)	0·2784
Red-blood-cell transfusions	116/286 (41)	148/291 (51)	134/288 (47)	150/291 (52)	0·0312
Platelet transfusions	7/285 (2)	13/290 (4)	9/286 (3)	11/289 (4)	0·5840
Antibiotics—interventional	131/288 (45)	161/291 (55)	151/285 (53)	180/289 (62)	0·0008

Data are numbers of patients with toxicity or therapeutic intervention/number of patients with information and percentage of patients. p values are over all treatment regimens. *Common Toxicity Criteria grade 4 only.

***Table 4*: Grade 3 and 4 Common Toxicity Criteria toxicities and therapeutic interventions**

3-year event-free survival of 66·8% (95% CI 53·1–80·5; n=59) after eight cycles of CHOP-14, 70·2% (55·5–84·9; n=38) after eight cycles of R-CHOP-14, 73·5% (61·0–86·0; n=53) after six cycles of CHOP-14, and 83·6% (72·4–94·8; n=46) after six cycles of R-CHOP-14, justifying their inclusion into this trial.

Adherence to the protocol was good: median relative doses for the myelosuppressive drugs were 98% or more (range 1–118) for the six-cycle regimens and 95% or more (range 7–111) for the eight-cycle regimens, and median duration of chemotherapy cycles was 14 days (range 8–92) in all regimens and cycles. As shown in figure 5, there were more dose reductions and treatment delays in the eight-cycle regimens than in the six-cycle regimens, but no difference between treatment regimens with and without rituximab.

We recorded higher proportions of patients with anaemia, mucositis, red-blood-cell transfusions, and interventional antibiotics in the two regimens with eight chemotherapy cycles than in the six-cycle regimens (table 4). There were 92 treatment-related deaths, 50 deaths in the 609 patients (8%) in the eight-cycle regimens and 42 deaths in the 613 patients (7%) in the six-cycle regimens. Except for one myocardial infarction and five thromboembolic events, all treatment-related deaths were due to infection. Patients assigned to eight cycles of R-CHOP-14 had more deaths not due to treatment, ie, lymphoma or secondary malignancies, than those assigned to six cycles of R-CHOP-14 (14 deaths in 304 [5%] patients *vs* 6 deaths in 306 [2%] patients). After the median observation time of 34·5 months, 62 second malignancies, including 51 solid tumours and six myelodysplastic syndromes or acute myelogenous leukaemias were reported, with no difference between treatment regimens. The incidence of secondary malignancies was not significantly different between patients assigned to radiotherapy (35 of 656 [5%] patients) or no radiotherapy (27 of 566 [5%] patients, p=0·6536).

Discussion

To our knowledge, this trial is the first randomised study to compare six and eight cycles of chemotherapy and assess the role of rituximab in combination with a dose-dense CHOP-14 regimen. Of the three intensified

regimens, only six cycles of R-CHOP-14, but not eight cycles of R-CHOP-14, improved event-free survival, progression-free survival, and overall survival over six cycles of CHOP-14. 3-year overall survival of eight cycles of R-CHOP-14 was 5·6% lower than after six cycles of R-CHOP-14. This finding can be explained by the higher proportion of treatment-associated deaths in patients assigned to eight-cycle treatment plus rituximab than six-cycle treatment plus rituximab (8% *vs* 5·6%) and by more deaths not due to treatment, ie, lymphoma or secondary malignancies (5% *vs* 2%). The proportion of overall treatment-associated deaths (ie, 8%) in this trial is higher than that after eight cycles of R-CHOP-21 in the French trial (6%),[3] and higher than that after six cycles of CHOP-14 in the preceding Non-Hodgkin Lymphoma-B2 (NHL-B2) trial (3%).[4] Whether this finding is because many patients in the RICOVER-60 trial received G-CSF starting on day 6 rather than on day 4 (as in the NHL-B2 trial), is unclear. In a parallel study in which 109 patients received the same treatment as in the RICOVER-60 trial and were additionally randomly assigned to receive pegfilgrastim on day 2 or 4, treatment-associated deaths occurred in fewer than 4% of patients.[10]

The role of additional radiotherapy to treat bulky disease and sites of extranodal involvement in patients assigned to radiotherapy (54% of patients) is unclear and was not studied in this trial. Meanwhile, 150 elderly patients with a risk profile very similar to that of patients in the RICOVER-60 trial have received six cycles of R-CHOP-14 without radiotherapy in a subsequent phase II study (Pfreundschuh M, unpublished data). The proportion of patients with complete responses in the first 50 evaluable patients was 88% (95% CI 79–97) and, therefore, not worse than the 78% (73–82) of patients assigned to six cycles of R-CHOP-14 in the RICOVER-60 trial, suggesting that the effect of radiotherapy in these patients is marginal, if existing at all.

To our knowledge, the high median relative doses in the six-cycle (≥98%) and eight-cycle (≥95%) regimens are the best ever reported for (bi-weekly and three-weekly) CHOP in a nationwide trial. This good adherence to dose-dense CHOP-14 chemotherapy was in part due to two measures, a pre-phase treatment (consisting of 1 mg of vincristine and 100 mg of prednisone starting about 1 week before the first CHOP-cycle) and hydrocortisone substitution. The pre-phase treatment had been introduced in the previous NHL-B2 trial by the DSHNHL[4] because many elderly patients who present with poor performance status and are not deemed suitable for CHOP, greatly improve during pre-phase treatment and become eligible for intensive chemotherapy. Furthermore, since the introduction of pre-phase treatment, first-cycle effect (ie, the phenomenon in which leucocyte nadirs are lowest and treatment-associated deaths are highest after the first cycle of chemotherapy) and tumour lysis syndrome are no longer seen. In our previous trial in elderly patients,[4] the (measurable) toxicity of CHOP-14 was not different from that of CHOP-21 and there is no reason to assume that it should be different after the addition of rituximab. Fatigue before the next chemotherapy cycle, which was reported more often by patients assigned to bi-weekly than three-weekly CHOP in that trial, can be treated in most patients by substituting hydrocortisone (20 mg in the morning and 10 mg in the early afternoon) after tapering prednisone. With these measures, treatment with CHOP-14 is feasible and well-tolerated in elderly patients. That 203 participating institutions recruited about one-third of the elderly population with DLBCL in Germany during the last 2 years of the trial, proves that CHOP-14 treatment is well-tolerated in a non-selected population of elderly patients aged between 61 and 80 years.

While the median doses in all four regimens of the current trial were 95% or more, the cumulative dose plots (figure 5) show more dose reduction in the eight-cycle than in the six-cycle regimens. Since such dose plots are more informative of protocol adherence than are median relative doses, they should be the standard format for reporting protocol adherence.

In the RICOVER-60 trial, IPI separated the 1222 patients into four significantly different risk groups, with and without rituximab. Therefore, by contrast to a publication that included only 365 patients,[11] there is no need to revise IPI. In our current trial, addition of rituximab improved the outcome in all risk groups. We included patients with stage I non-bulky disease because in our previous NHL-B1 trial these patients had no better outcome than patients with stage II non-bulky disease. The findings from these patients in the RICOVER-60 trial reported here show that these patients were not overtreated and their inclusion in this trial was justified.

The proportion of patients with complete response after six cycles of R-CHOP-14 was 2% better than after eight cycles of R-CHOP-14. This is explained by the higher number of treatment-associated deaths (table 2) after eight cycles of R-CHOP-14. Six cycles of R-CHOP-14 was at least as good as eight cycles of R-CHOP-14 in any of the four risk groups according to IPI[12] (figure 3). Eight cycles of CHOP-14 improved event-free survival over six cycles, but not progression-free survival or overall survival, suggesting that additional treatment without progression (which was counted as an event in event-free survival only) was given more often in the least intensive of the four treatment regimens. An important observation from this randomised comparison between six and eight chemotherapy cycles is that adjusting the number of chemotherapy cycles for an individual patient based on interim restaging results—though widely practised—is not justified because six cycles of R-CHOP-14 was as good as eight cycles of R-CHOP-14, irrespective of whether patients were in complete response, unconfirmed complete response, or partial response at mid-treatment restaging (figure 4); this finding applied to patients with and without radiotherapy. While this observation was

made with bi-weekly R-CHOP-14, it should also apply to treatment with R-CHOP-21, where responses (and chemotherapy resistances) have more time (12 weeks instead of 8 weeks) to evolve and, therefore, should be even less amenable to treatment modifications at mid-treatment than in bi-weekly regimens. Additionally, whether interim PET scans, which have been shown to predict prognosis,[13] are better than use of CT scans for tailoring of treatment to individual patients remains yet to be shown.

RICOVER-60 is the largest trial in aggressive CD20+ B-cell lymphomas. In addition to DLBCL with its variants and subgroups, follicular lymphoma grade 3, follicular lymphoma grade 3 and DLBCL, blastic mantle cell, aggressive marginal zone lymphoma, and Burkitt and Burkitt-like lymphoma were eligible for this trial. A sensitivity analysis showed that the findings of all 1222 patients did not differ from those obtained if the analysis was restricted to patients with DLBCL only (with a tendency of better findings for patients with DLBCL in all four treatment regimens).

The findings obtained with six cycles of CHOP-14 plus eight cycles of rituximab are the best reported to date for elderly patients with DLBCL. Although the interval reduction from 3 weeks to 2 weeks[4] and the addition of rituximab to three-weekly CHOP-21[3] achieved similar improvements over classical CHOP-21, our RICOVER-60 trial showed that further improvement is possible by combining interval reduction with rituximab. The improvement achieved by the addition of rituximab to CHOP-14 is smaller than by the addition of rituximab to the three-weekly CHOP-21;[3,14] in particular, the gain in overall survival is restricted, and compared with six cycles of CHOP-14, just reached significance for six cycles of R-CHOP-14 (p=0·0181), but not for eight cycles of R-CHOP-14 (p=0·2602). Part of this modest gain in overall survival might be due to the fact that rituximab was available for DLBCL patients during the last 3 years of the trial's recruitment period and many patients failing on the CHOP-14 regimens without rituximab received the antibody as part of their salvage treatment.

Another difference between adding rituximab to CHOP-14 and CHOP-21 is the observation that high-risk patients benefit at least as much as low-risk patients from the addition of rituximab to CHOP-14. This is in contrast to the Groupe d'Etude des Lymphomes de l'Adulte (GELA) study[3,14] in which the effect of rituximab was more pronounced in low-risk than in high-risk patients, and might be explained by the fact that with R-CHOP-14, not only chemotherapy, but also rituximab is given in a dose-dense fashion, rendering the antibody more potent in high-risk, ie, fast-growing tumours or large tumour masses.

Findings of our pharmacokinetic study of rituximab with CHOP-14[15] show that even with the twice-weekly regimen, plateau trough levels of rituximab are not reached until after five cycles (or 10 weeks) of treatment. Model calculations predict that with a three-weekly application,[3,16] the increment of rituximab serum concentrations is even slower (six cycles or 18 weeks) and associated with a lower plateau.

While the RICOVER-60 trial showed that R-CHOP-14 was better than CHOP-14 alone, the efficacy of R-CHOP-14 over R-CHOP-21 remains to be shown. The GELA is currently assessing this question in the NHL-03-6B trial, in which eight cycles of R-CHOP-21 is being compared with eight (but not six) cycles of R-CHOP-14 treatment in elderly patients. The National Cancer Research Institute, London, UK, is comparing eight cycles of R-CHOP-21 with six cycles of R-CHOP-14 in patients with DLBCL of any age and risk group. The difference between the patients in our current trial and the GELA trial is the inclusion of patients with stage I disease in our study, which is justified by their outcome reported here. After exclusion of these patients, the populations included in the two respective trials—RICOVER 60 and the ongoing GELA—are virtually identical. Even if the ongoing GELA and NCRI trials were to show equal efficacy for R-CHOP-14 and R-CHOP-21, six cycles of R-CHOP-14 has the advantage over eight cycles of R-CHOP-21 because it affords cessation of chemotherapy in half the time, and thus contributes an important gain in quality of life for these elderly patients, for whom prolonged treatment protocols are especially arduous. Therefore, the favourable toxicity profile of six cycles of bi-weekly R-CHOP-14, which was no more toxic than three-weekly R-CHOP-14,[4,17] makes six cycles of R-CHOP-14 the preferred option of the four treatment regimens studied in this trial for elderly patients, and to which other approaches should be compared.

Contributors

MP was the study chairman. JS was the scientific coordinator. RS was the medical consultant. MP, LT, FH, BG, ML, and NS designed the study. MM, EL, CN, MC, NP, CB, HE, AH, MH, RM, LT, LB, RL, and BM recruited patients and discussed the report. BG also recruited patients. FH and NS also discussed the report. MP, MZ, and ML were responsible for writing the report. MZ and ML did the statistical analysis. MR did the pharmacokinetic studies. VP was responsible for medical coordination and data monitoring. CR coordinated and evaluated radiotherapy. ACF coordinated the reference pathology. JS and MZ contributed equally.

RICOVER-60 trial members

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Conflicts of interest

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