Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial

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Summary

Background Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has become the standard of care for elderly patients with diffuse large B-cell lymphoma. We aimed to ascertain if a dose-dense R-CHOP regimen administered every 2 weeks (R-CHOP14) was superior to the standard 3-week schedule (R-CHOP21).

Methods We did a randomised phase 3 trial at 83 centres in four countries. 602 patients aged 60–80 years with untreated diffuse large B-cell lymphoma and at least one adverse prognostic factor (age-adjusted international prognostic index ≥1) were eligible for the study. We randomly allocated individuals to R-CHOP—ie, rituximab (375 mg/m²), cyclophosphamide (750 mg/m²), doxorubicin (50 mg/m²), vincristine (1·4 mg/m², up to 2 mg) all on day 1, and prednisone 40 mg/m² daily for 5 days—administered every 14 days (n=304) or every 21 days (n=298) for eight cycles. We did permuted-block randomisation (block size four, allocation ratio 1:1) stratified by centre and number of adverse prognostic factors. The primary endpoint was event-free survival. Our analysis was of the intention-to-treat population, and we present the final analysis. This study is registered with ClinicalTrials.gov, number NCT00144755.

Findings Two patients allocated R-CHOP21 were ineligible for the study and were excluded from analyses. After median follow-up of 56 months (IQR 27–60), 3-year event-free survival was 56% (95% CI 50–62) in the R-CHOP14 group and 60% (55–66) in the R-CHOP21 group (hazard ratio 1·04, 95% CI 0·82–1·31; p=0·7614). Grade 3–4 neutropenia occurred in 224 (74%) of 304 patients allocated R-CHOP14 and 189 (64%) of 296 assigned R-CHOP21, despite increased use of granulocyte colony-stimulating factor in the R-CHOP14 group compared with the R-CHOP21 group. 143 (47%) patients in the R-CHOP14 group received at least one red-blood-cell transfusion versus 93 (31%) in the R-CHOP21 group (p=0·0001). 35 (12%) patients allocated R-CHOP14 received at least one platelet transfusion versus 25 (8%) assigned R-CHOP21 (p=0·2156). 155 (51%) patients who were assigned R-CHOP14 had at least one serious adverse event compared with 140 (47%) who were allocated R-CHOP21.

Interpretation In elderly patients with untreated diffuse large B-cell lymphoma and at least one adverse prognostic factor, a 2-week dose-dense R-CHOP regimen did not improve efficacy compared with the 3-week standard schedule. The frequency of toxic side-effects was similar between regimens, but R-CHOP14 was associated with increased need for red-blood-cell transfusion.

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A full list of trial investigators can be found in the appendix

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Introduction

Diffuse large B-cell lymphoma is the most common subtype of non-Hodgkin lymphoma, accounting for about 25% of all lymphoid neoplasms.[1] More than half of affected patients are older than 60 years at diagnosis, and treatment of this group remains a challenge.

The introduction of rituximab in the past decade, and its combination with classic CHOP (doxorubicin, cyclophosphamide, vincristine, and prednisone) chemotherapy, has greatly improved patients' outcome.[2,3] Findings of three prospective randomised studies undertaken in elderly populations (aged 60–80 years) established immunochemotherapy as standard.[4–6] In a GELA (Groupe d'Etude des Lymphomes de l'Adulte) study,[4] and a US Intergroup study,[5] rituximab was administered with classic CHOP21 (3-week cycle).[7] In the German Ricover-60 study,[6] rituximab was added to dose-dense CHOP14 (2-week cycle), since previous work[8] showed that CHOP14 (without rituximab) was associated with improved progression-free and overall survival compared with CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma.

To assess the effect of dose-dense immunochemotherapy for patients aged 60–80 years with untreated diffuse large

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B-cell lymphoma, we designed a randomised phase 3 study in 2003, to compare eight cycles of R-CHOP14 with eight cycles of R-CHOP21. Here, we present the final analysis.

Methods

Study design and patients

We designed a phase 3, multicentre, randomised trial to compare the efficacy of two schedules of immunochemotherapy, with or without prophylactic darbepoetin alfa, in elderly patients with untreated diffuse large B-cell lymphoma. The study was undertaken at 83 centres in France, Belgium, Switzerland, and Portugal. Eligible participants underwent two randomisation procedures. In the first, we allocated one of two chemotherapy regimens—ie, R-CHOP given every 14 (R-CHOP14) or 21 (R-CHOP21) days. In the second, we randomly assigned patients to a standard arm with conventional management of chemotherapy-induced anaemia or to an experimental arm with prophylactic darbepoetin alfa. This second randomisation was stratified by chemotherapy regimens and will be presented elsewhere.

We judged people eligible if they were aged 66–80 years and had untreated diffuse large B-cell lymphoma. After closure of the GELA LNH 01-5B study (NCT00135499), which included individuals aged 60–65 years, we amended (on Dec 1, 2005) the age range for eligibility to 60–80 years. Furthermore, patients also needed at least one adverse prognostic factor on the age-adjusted international prognostic index and a good performance status (Eastern Cooperative Oncology Group 0–2). Additional inclusion criteria were a life expectancy of at least 3 months and negative serological tests for HIV and hepatitis B and C virus in the past 4 weeks (except after vaccination for hepatitis B virus).

People were not eligible if they had any other histological type of lymphoma or any history of treated or non-treated indolent lymphoma. However, we could have included individuals not previously diagnosed with diffuse large B-cell lymphoma but who had diffuse large B-cell lymphoma with small-cell infiltration in bone marrow or lymph nodes. Other exclusion criteria were CNS or meningeal involvement by lymphoma, contraindication to any drug in the chemotherapy regimens, any serious comorbid active disease (investigator's decision), or any history of cancer during the past 5 years, with the exception of non-melanoma skin tumours or in-situ cervical carcinoma. Unless these abnormalities were related to lymphoma, we also excluded patients with poor renal function (creatinine concentration >150 μmol/L), hepatic disorders (total bilirubin >30mmol/L or aminotransferases >2·5 times the maximum normal amount), or poor bone marrow reserve (neutrophil count <1·5×10⁹ per L or platelet count <100×10⁹ per L). Finally, we prohibited treatment with any investigational drug within 30 days before the planned first cycle of chemotherapy and during the study.

Local or national ethics committees approved the study protocol, according to the laws of every country. The study was done in accordance with the Declaration of Helsinki. Patients provided written informed consent before inclusion.

Randomisation and masking

We used computer-assisted permuted-block randomisation (block size of four, allocation ratio 1:1) to assign treatment. Randomisation was stratified by participating centre and age-adjusted international prognostic index (1 *vs* 2 or 3). A statistician located centrally at the GELA research clinic supervised the randomisation procedure. The treatment allocation was sent to the investigator by fax. Investigators and patients were not masked to treatment assignment.

Procedures

We planned for patients to receive eight cycles of the R-CHOP regimen—ie, a combination of intravenous rituximab (375 mg/m²), cyclophosphamide (750 mg/m²), doxorubicin (50 mg/m²), vincristine (1·4 mg/m², up to 2 mg) all on day 1, and oral prednisone 40 mg/m² daily for 5 days—every 14 or 21 days. All patients received neuromeningeal prophylaxis of four consecutive intrathecal injections of methotrexate (15 mg) every 14 or 21 days. We gave granulocyte colony-stimulating factor (pegylated or not), according to the treating doctor's decision, fulfilling existing guidelines and product labelling at that time. We did not allow radiotherapy.

We made no dose adjustments for haematological toxic effects. However, we postponed the next cycle of R-CHOP until neutrophil counts reached 1·5×10⁹ per L and platelet counts 100×10⁹ per L. If grade 1 neurological toxic effects arose, we reduced the dose of vincristine to 1 mg per cycle. If neurological toxic effects continued despite a decrease in dose, we stopped vincristine. We allowed use of concomitant antimicrobial chemoprophylaxis with co-trimoxazole or valaciclovir, at the investigator's discretion.

Initial staging included physical examination, standard laboratory assessments, CT of the chest, abdomen, and pelvis, cerebrospinal fluid examination, and bone marrow biopsy. We did not regard ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET as mandatory for staging or assessment of response to treatment. We defined stage of lymphoma in accordance with the Ann Arbor classification. We classed bulky disease as any mass of 10 cm or greater at the maximum diameter. We assessed performance status with the Eastern Cooperative Oncology Group scale. At least two pathologists at the GELA pathology centre reviewed specimens to confirm the diagnosis of CD20-positive diffuse large B-cell lymphoma. Tumours were classified in accordance with the WHO classification.[9]

The local investigator assessed response rates after the first four cycles and either at the end of treatment,

4 weeks after the eighth cycle, or on withdrawal (if premature). We classified patients according to international criteria.[10] The local investigator followed up patients every 3 months in the first 2 years and every 6 months thereafter. We did physical examination and laboratory tests at every visit and CT every 6 months during the first 2 years, and yearly thereafter.

We reported all toxic effects during the treatment phase and for 3 months after completion of treatment. We asserted that all grade 3 and 4 toxic effects (using the National Cancer Institute's common toxicity criteria grading system, version 4.0), or grade 2 for infections, and all toxic effects (grade 1–4) related to a serious adverse event had to be reported as an adverse event, with the exception of alopecia and haematological toxicities without fever. We defined serious adverse events as any event resulting in death or a life-threatening condition, requiring admission or prolongation of existing admission, or resulting in persistent or substantial disability or incapacity or inducing a congenital anomaly or birth defect. We reported all such defined serious adverse events that arose up to 3 months after completion of treatment.

Our primary endpoint was event-free survival. We measured event-free survival from the date of randomisation to the date of the first event. We defined events as either disease progression during or after (for partial responders) treatment, relapse for complete or unconfirmed complete responders, death from any cause, or introduction of a new treatment without evidence of progression or relapse (including radiotherapy), whichever occurred first.

Secondary endpoints included response rate, progression-free survival, disease-free survival, overall survival, and toxic effects. We measured progression-free survival from the date of random assignment to either progression or relapse or death from any cause. We classed disease-free survival from the time of attainment of a complete or unconfirmed complete response to disease recurrence or death caused by lymphoma or treatment-related toxic effects. We calculated overall survival from the date of random assignment to the date of death from any cause.

Statistical analysis

We calculated sample size on the basis of the primary endpoint. In the previous GELA trial, in which patients older than 60 years were included,[4] the 2-year estimate of event-free survival was 55% for R-CHOP21. To detect a change in 2-year event-free survival in the experimental arm, from 55% to 65%, we needed 600 patients (300 events), randomised in a 1:1 ratio, recruited over 4 years, and followed up for a minimum of 1 year to provide 80% power at an overall 5% (two-sided) significance level. We planned an interim analysis after 2 years (90 events) and minimum follow-up of 1 year.

We used a group sequential approach to define early-stopping rules (α spending function with the O'Brien-Fleming method). We calculated significance thresholds to adjust type I error attributable to multiple comparisons (α of 0·0001 and 0·05, respectively, for interim and final analyses). The data and safety monitoring committee assessed the results of the interim analysis.

For every drug, we calculated the relative dose intensity for patients who received the first four cycles and for those who received the planned eight cycles. We measured the duration of treatment as the interval between the first day of treatment and either the last day of the fourth cycle (respectively, 56 days and 84 days for R-CHOP14 and R-CHOP21) or the last day of the seventh cycle (98 days and 148 days, respectively). We did not include patients in either analysis who withdrew from the study (whatever the cause) before these endpoints. We also assessed the relative dose intensity for all cycles in all patients (except those who withdrew before cycle two). Finally, in the R-CHOP14 arm, we calculated relative dose intensity by 3-week intervals, to assess the increase compared with 2-week intervals.

We analysed data according to the intention-to-treat principle. The intention-to-treat population included all patients, irrespective of the availability of pathological

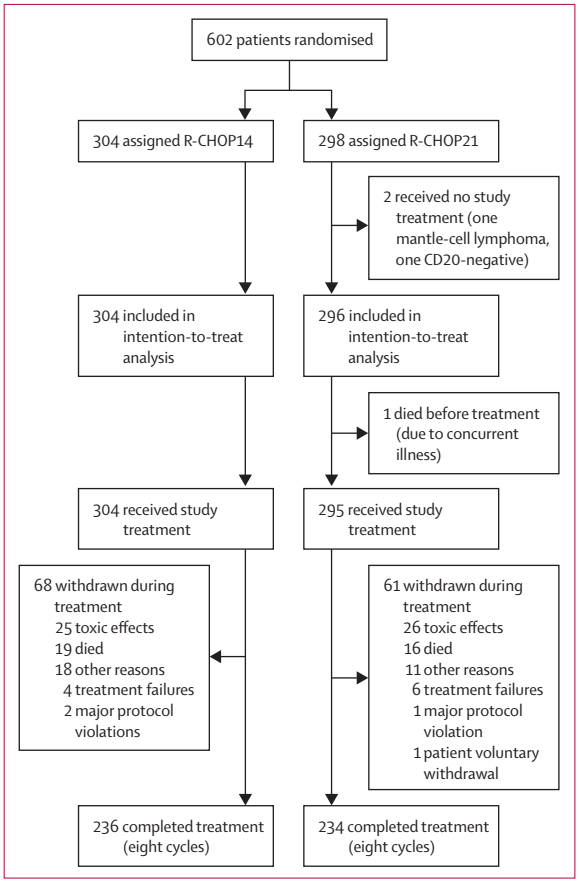

Figure 1: **Trial profile**

review. We compared patients' characteristics, response rates, and prevalence of transfusion with the χ^2 or Fisher's exact test. We estimated survival functions with the Kaplan-Meier method and compared them using the log-rank test. We calculated hazard ratios and 95% CIs by Cox proportional-hazards analysis. We used Student's *t* test to compare the relative dose intensity and the Mann-Whitney-Wilcoxon test for nights of admission. We judged differences significant if p values were less than 0·05 (two-sided). We did all statistical analyses with SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

	R-CHOP14 (n=304)	R-CHOP21 (n=298)
Sex		
Male	169 (56%)	165 (55%)
Female	135 (44%)	133 (45%)
Age (years)	70 (60–80)	70 (59–80)
ECOG performance status		
0–1	247 (81%)	220 (74%)
≥2	57 (19%)	78 (26%)
B symptoms present*	108 (36%)	115 (39%)
Ann Arbor stage		
I–II	35 (12%)	36 (12%)
III–IV	269 (88%)	262 (88%)
Bulky mass >10 cm	51 (17%)	53 (18%)
Serum lactate dehydrogenase above normal laboratory values	200 (66%)	212 (71%)
β2 microglobulin†		
<3 mg/L	144 (57%)	133 (53%)
≥3 mg/L	108 (42%)	118 (47%)
Albumin‡		
>35 g/L	180 (66%)	174 (66%)
≤35 g/L	93 (34%)	91 (34%)
Extranodal sites		
0–1	160 (53%)	135 (45%)
>1	144 (47%)	163 (55%)
Bone-marrow involvement		
No	223 (73%)	217 (73%)
Yes	62 (20%)	66 (22%)
Not assessed or unspecified	19 (6%)	15 (5%)
IPI		
0–2	84 (28%)	65 (22%)
3	104 (34%)	98 (33%)
4–5	116 (38%)	135 (45%)
Age-adjusted IPI		
0–1	118 (39%)	103 (35%)
2	146 (48%)	130 (44%)
3	40 (13%)	65 (22%)
Histology		
Diffuse large B-cell lymphoma	260 (86%)	254 (85%)
Other diagnosis, or unclassified	18 (6%)	11 (4%)
Not reviewed	26 (9%)	33 (11%)

Data are number of patients (%) or median (range). *Night sweats, loss of weight, fever. †Data missing for 52 patients in the R-CHOP14 group and 47 in the R-CHOP21 group. ‡Data missing for 31 patients in the R-CHOP14 group and 33 in the R-CHOP21 group. ECOG=Eastern Cooperative Oncology Group. IPI=international prognostic index.

Table 1: **Baseline characteristics**

Role of the funding source

Workers at the GELA research clinic undertook data monitoring, study coordination, and data analysis; they did the randomisation, undertook distribution and collection of case report forms, assisted data entry and validation, coordinated monitoring procedures, helped with elaboration and mailing of queries, reported serious adverse events, coordinated histological review, maintained relations with investigators, transmitted enrolment status to the sponsor, did statistical analysis, and wrote the report. Amgen had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between December, 2003, and November, 2008, 602 patients were enrolled and underwent random assignment. 304 individuals were allocated to the R-CHOP14 group and 298 were assigned to the R-CHOP21 group (figure 1). One patient was diagnosed with mantle-cell lymphoma and one with CD20-negative lymphoma before treatment began and were therefore excluded from analyses. Thus, 600 patients were included in the intention-to-treat analysis. One individual died before treatment started due to concurrent illness; thus, 599 people received study treatment.

Central pathological review was available for 531 (88%) of 602 patients. The diagnosis of diffuse large B-cell lymphoma, according to the 2008 WHO classification, was confirmed for 514 (97%) patients.

Table 1 presents baseline characteristics of patients. Overall, the median age of the study population was 70 years (IQR 66–74) and 334 (55%) patients were men. Most people presented at diagnosis with either disseminated disease or raised amounts of lactate dehydrogenase, or both. 186 (61%) patients in the R-CHOP14 group and 195 (65%) in the R-CHOP21 group had poor prognosis (age-adjusted international prognostic index of 2 or 3). More patients in the R-CHOP21 group presented with a performance status greater than 1 and had at least one extranodal site. Furthermore, a higher proportion of patients in the R-CHOP21 group had three adverse prognostic factors and an international prognostic index of 4–5, compared with those in the R-CHOP14 group.

236 (78%) of 304 patients in the R-CHOP14 group and 234 (79%) of 298 people in the R-CHOP21 group received all eight scheduled cycles of chemotherapy (figure 1). The median interval between two cycles in the R-CHOP14 group was 14 days (range 9–84), compared with 21 days

(15–66) in the R-CHOP21 group. In 49 (16%) patients assigned to the R-CHOP14 group, the median time between induction cycles was longer than 18 days; this 33% increase could be judged a hallmark of failure to obtain a correct interval between cycles.

Patients in both arms received a lower relative dose intensity than expected, with a higher proportion noted in the R-CHOP14 group (table 2). In individuals who received eight planned treatment cycles (236 in the R-CHOP14 group and 234 in the R-CHOP21 group), the median relative dose intensity for cyclophosphamide was 88% (IQR 79–93) in the R-CHOP14 group and 97% (93–99) in the R-CHOP21 group (p<0·0001); for doxorubicin, median relative dose intensity was 88% (78–94) and 96% (92–99), respectively (p<0·0001). The same analysis was done for all patients who received the first four cycles of treatment (275 in the R-CHOP14 group and 269 in the R-CHOP21 group), and findings were similar: median relative dose intensity of cyclophosphamide was 88% (79–96) in the R-CHOP14 group and 98% (92–100) in the R-CHOP21 group (p<0·0001); for doxorubicin, values were 88% (78–96) and 98% (92–100), respectively (p<0·0001). Finally, we analysed relative dose intensity for all patients who received at least two treatment cycles (296 in the R-CHOP14 group and 286 in the R-CHOP21 group): the median relative dose intensity was 87% (76–93) in the R-CHOP14 group and 96% (92–99) in the R-CHOP21 group (p<0·0001); for doxorubicin, it was 87% (76–93) and 96% (90–99), respectively (p<0·0001). Using the 3-week interval as a reference, patients in the R-CHOP14 group received a relative dose intensity of 134% for both drugs.

Granulocyte colony-stimulating factor was given during 1949 of 2196 cycles of R-CHOP14 and 1502 of 2150 cycles of R-CHOP21 (table 3). 222 (73%) patients in the R-CHOP14 group received granulocyte colony-stimulating factor from the first cycle as primary prophylaxis. Median relative dose intensity for cyclophosphamide and doxorubicin did not differ by use of granulocyte colony-stimulating factor at the first cycle in the R-CHOP14 group (data not shown).

After median follow-up of 56 months (IQR 27–60), 143 (47%) patients in the R-CHOP14 group and 140 (47%) in the R-CHOP21 group presented with an event. Two-thirds of events were progression or relapse (table 4). 3-year event-free survival (figure 2A) was similar between the R-CHOP14 and R-CHOP21 groups (56% [95% CI 50–62] *vs* 60% [55–66], respectively; hazard ratio 1·04, 95% CI 0·82–1·31; p=0·7614). Median event-free survival was 68·6 months (95% CI 41·7 to not estimable [NE]) in the R-CHOP14 group and 53·6 (45·6 to NE) in the R-CHOP21 group.

A complete or unconfirmed complete response at the end of treatment was achieved in 216 (71%) patients in the R-CHOP14 group and 220 (74%) in the R-CHOP21 group. Overall responses were noted in 268 (87%) and 257 (86%) patients, respectively (p=0·6214).

	R-CHOP14 (n=304)		R-CHOP21 (n=295)	
	Cyclophosphamide	Doxorubicin	Cyclophosphamide	Doxorubicin
<80%	67 (22%)	71 (23%)	20 (7%)	29 (10%)
≥80% to <85%	37 (12%)	36 (12%)	27 (9%)	26 (9%)
≥85% to <90%	51 (17%)	49 (16%)	16 (5%)	22 (7%)
≥90% to <95%	75 (25%)	72 (24%)	67 (23%)	61 (21%)
≥95%	74 (24%)	76 (25%)	165 (56%)	157 (53%)

Data are number of patients (%).

Table 2: **Final relative dose intensity of cyclophosphamide and doxorubicin, by treatment arm**

	R-CHOP14	R-CHOP21
Cycle 1	222/304 (73%)	178/296 (60%)
Cycle 2	266/296 (90%)	189/286 (66%)
Cycle 3	264/288 (92%)	196/284 (69%)
Cycle 4	261/284 (92%)	199/276 (72%)
Cycle 5	252/275 (92%)	195/269 (72%)
Cycle 6	247/266 (93%)	196/261 (75%)
Cycle 7	223/247 (90%)	175/244 (72%)
Cycle 8	214/236 (91%)	174/234 (74%)

Data are number of patients (%). Denominators differ per cycle because of premature withdrawals.

Table 3: **Use of granulocyte colony-stimulating factor during every cycle**

	R-CHOP14 (n=304)	R-CHOP21 (n=296)
No event	161 (53%)	156 (53%)
New treatment without progression*	21 (7%)	11 (4%)
Chemotherapy	12	8
Radiotherapy	6	5
Immunotherapy	9	8
Transplant	2	1
Other	1	1
Progression or relapse	87 (29%)	90 (30%)
Death without progression	35 (12%)	39 (13%)

*Patients could have received more than one treatment.

Table 4: **Analysis of events for event-free survival**

3-year progression-free survival did not differ between the R-CHOP14 and R-CHOP21 groups (60% [95% CI 54–65] *vs* 62% [56–67], respectively; hazard ratio 0·99, 95% CI 0·78–1·26; p=0·8983; figure 2B). Estimated 5-year progression-free survival was 53% (95% CI 47–59) and 49% (43–56), respectively. Median progression-free survival had not been reached (95% CI 47·3 to NE) in the R-CHOP14 group and was 59·0 months (48·5 to NE) in the R-CHOP21 group. Disease-free survival at 3 years was also similar between the R-CHOP14 group (72% [95% CI 66–78]) and the R-CHOP21 group (67% [61–73]; hazard ratio 0·80, 95% CI 0·58–1·10; p=0·1640; figure 2C). Median disease

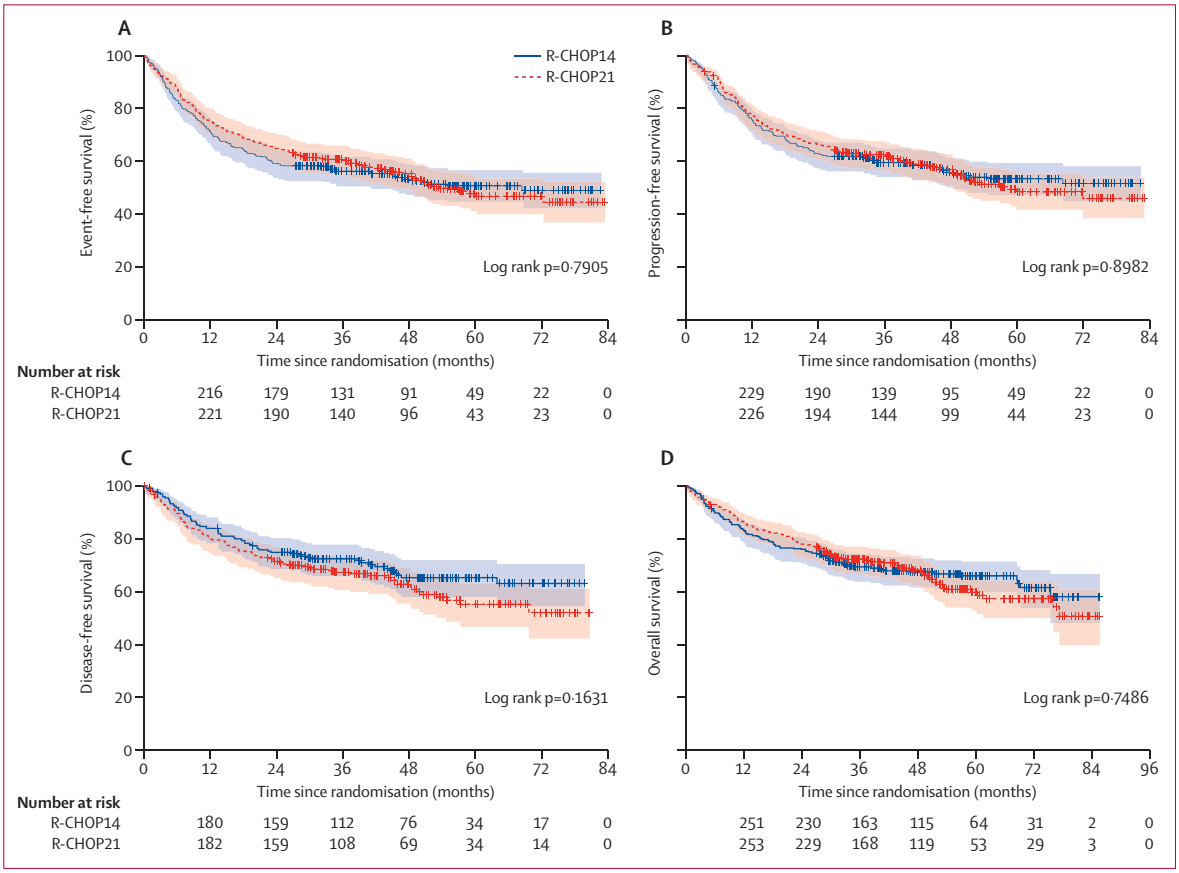

Figure 2: **Survival endpoints**
(A) Event-free survival. (B) Progression-free survival. (C) Disease-free survival. (D) Overall survival. Shaded areas show 95% CIs.

	R-CHOP14 (n=106)	R-CHOP21 (n=109)
Lymphoma	54 (51%)	57 (52%)
Toxic effects of study treatment	14 (13%)	14 (13%)
Concurrent illness	20 (19%)	13 (12%)
Other cancer	9 (8%)	14 (13%)
Toxic effects of additional treatment	2 (2%)	5 (5%)
Other reason, or reason unknown	7 (7%)	6 (6%)

Table 5: **Causes of death**

free-survival had not been reached in the R-CHOP14 group (95% CI NE to NE), nor had it been reached in the R-CHOP21 group (54·7 to NE). Finally, 3-year overall survival was 69% (95% CI 64–72) in the R-CHOP14 group versus 72% (67–77) in the R-CHOP21 group (hazard ratio 0·96, 95% CI 0·73–1·26; p=0·7487; figure 2D). Estimates of 5-year overall survival were 66% (95% CI 60–71) and 60% (53–66), respectively. Table 5 shows causes of death. Median overall survival had not been reached in the R-CHOP14 group (95% CI 75·4 to NE) and had also not been reached in the R-CHOP21 group (76·1 to NE).

We did a multivariate Cox analysis (appendix), including treatment arm, group allocation for prophylactic darbepoetin alfa, age, individual factors of the international prognostic index, bone marrow involvement, β2 microglobulin, albumin, and bulky disease (441 available observations). Neither randomisation arm—for either immunochemotherapy or prophylactic darbepoetin alfa—was predictive for progression-free or overall survival. Age older than 70 years, raised amounts of lactate dehydrogenase, altered performance status, and β2 microglobulin were predictive for poorer progression-free and overall survival. Future analyses will include correlations of outcome with pathological and biological factors.

We analysed safety for all patients who received at least one injection of study treatment, irrespective of the quantity injected. The prevalence of toxic effects was similar between treatment groups (table 6). The proportion of patients with at least one adverse or serious adverse event did not differ between R-CHOP14 and R-CHOP21 groups.

1303 adverse events in 454 (76%) of 599 patients were reported; 694 events were recorded in 235 patients assigned to R-CHOP14 versus 609 events in 219 individuals allocated R-CHOP21. Adaptation of the dosage regimen was needed

	R-CHOP14 (n=304)			R-CHOP21 (n=295)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Anaemia	296 (97%)	56 (18%)	12 (4%)	272 (92%)	42 (14%)	9 (3%)
Neutropenia	257 (85%)	46 (15%)	178 (59%)	244 (83%)	40 (14%)	149 (51%)
Thrombocytopenia	215 (71%)	27 (9%)	21 (7%)	185 (63%)	30 (10%)	28 (9%)
Febrile neutropenia	65 (21%)	64 (21%)	1 (<1%)	54 (18%)	54 (18%)	0
Infection (associated with neutropenia grades 3–4)	43 (14%)	30 (10%)	2 (<1%)	61 (21%)	35 (12%)	3 (1%)
Infection (no grade 3–4 neutropenia)	66 (22%)	17 (6%)	1 (<1%)	60 (20%)	13 (4%)	0
Nausea or vomiting	72 (24%)	3 (1%)	0	52 (18%)	3 (1%)	0
Diarrhoea	57 (19%)	0	1 (<1%)	57 (19%)	5 (2%)	1 (<1%)
Mucositis	90 (30%)	13 (4%)	2 (<1%)	76 (26%)	7 (2%)	3 (1%)
Cardiac-related	24 (8%)	2 (<1%)	2 (<1%)	27 (9%)	10 (3%)	1 (<1%)
Vascular-related	33 (11%)	13 (4%)	8 (3%)	31 (11%)	7 (2%)	7 (2%)
Rise in creatinine concentration	35 (12%)	2 (<1%)	0	34 (12%)	2 (<1%)	0
Increase in amount of liver enzymes	83 (27%)	3 (1%)	0	71 (24%)	3 (1%)	0
Neurological-related	105 (35%)	15 (5%)	1 (<1%)	94 (32%)	13 (4%)	3 (1%)
Skin-related	61 (20%)	4 (1%)	0	44 (15%)	0	1 (<1%)
Pulmonary-related	46 (15%)	1 (<1%)	1 (<1%)	55 (19%)	9 (3%)	1 (<1%)
Constitutional symptoms	190 (63%)	17 (6%)	0	159 (54%)	12 (4%)	2 (<1%)
Allergy	11 (4%)	0	0	12 (4%)	0	0
Other	218 (72%)	32 (11%)	12 (4%)	191 (65%)	34 (12%)	5 (2%)

Data are number of patients having an event (%). Patients could have the same type of event more than once.

Table 6: **Prevalence of toxic effects**

for 36 (12%) of 304 patients in the R-CHOP14 group and for 37 (13%) of 295 in the R-CHOP21 group. Finally, 49 (21%) of 235 patients with adverse events in the R-CHOP14 group and 42 (19%) of 219 with adverse events in the R-CHOP21 group permanently stopped at least one drug because of an adverse event. The most common adverse events were infections and infestations (438 events) and blood and lymphatic-system disorders (276 events), including 219 (17%) cases of febrile neutropenia. A total of 626 adverse events in 295 patients were reported as serious, 342 events in 155 patients assigned R-CHOP14 versus 284 events in 140 allocated R-CHOP21.

Haematological toxic effects were similar in both groups. Red-blood-cell transfusions were more common in the R-CHOP14 group: 143 (47%) patients assigned R-CHOP14 versus 93 (31%) allocated R-CHOP21 received at least one transfusion (p=0·0001). With respect to platelets, 35 (12%) patients in the R-CHOP14 group received at least one transfusion, compared with 25 (8%) in the R-CHOP21 group (p=0·2156).

The median number of nights admitted to hospital during the whole treatment phase was similar between groups. Overall, patients assigned R-CHOP14 spent 9 nights in hospital (IQR 2–20) compared with 7 nights (2–16) in those allocated R-CHOP21 (p=0·1227).

14 patients in each group died because of toxic effects related to study treatment (table 5). The main cause of death was infection (ten patients assigned R-CHOP14 and eight allocated R-CHOP21). Others causes of death in the R-CHOP14 group were small-bowel perforation (n=1), myocardial infarction (n=1), cardiac failure (n=1), and stroke (n=1). In the R-CHOP21 group, other causes of death were cardiac failure (n=1), stroke (n=1), acute myeloid leukaemia (n=1), respiratory failure (n=1), and suicide (n=2). Of patients who died because of treatment-related toxic effects, the median time between randomisation and death was 93 days (IQR 41–121) in the R-CHOP14 group and 49 days (19–145) in the R-CHOP21 group.

Discussion

Our findings did not show any difference in efficacy endpoints between dose-dense and standard regimens of R-CHOP in elderly patients with diffuse large B-cell lymphoma. Moreover, our results with R-CHOP21 accord with previous work.[4] Comparison of our findings with those of the German Ricover-60 study (panel)[6] should be made cautiously because the two study populations are not comparable with respect to prognostic factors: in the German study, patients were younger (median 68 years, *vs* 70 years in our study) and only 43% presented with an international prognostic index of 3 (*vs* 72% in our study). Patients in the German study could have received six or eight cycles of R-CHOP14, with no difference recorded in efficacy according to the number of cycles (although only six cycles of R-CHOP14 increased overall survival compared with CHOP14). Furthermore, 34% of patients received radiotherapy as a part of their treatment, whereas use of radiotherapy was deemed an event in our

Panel: **Research in context**

Systematic review

We searched Medline for full reports of randomised clinical trials with the terms "R-CHOP 14" and "diffuse large B-cell lymphoma". We identified only one study undertaken solely in elderly patients, in which R-CHOP14 was compared with CHOP, for six or eight cycles.[6] Thus, R-CHOP14 had previously not been assessed with other immunochemotherapy regimens containing rituximab for first-line treatment of elderly patients with diffuse large B-cell lymphoma.

Interpretation

R-CHOP14 administered for eight cycles is feasible in elderly patients with diffuse large B-cell lymphoma. However, the increased toxicity with the dose-dense regimen resulted in a lower relative dose intensity for patients receiving R-CHOP14 than those receiving R-CHOP21. As a result, we did not record a difference between eight cycles of R-CHOP14 and eight cycles of the classic R-CHOP21 schedule with respect to efficacy.

study, because no effect on outcome of consolidative radiotherapy is seen in this subgroup of patients.[11] A prephase of treatment was recommended before cycle one for all patients in the German study, yet pre-treatment was an exclusion criterion in our study. Finally, median follow-up was lower in the German study (34·5 months) than in our study. With these precautions in mind, our results are similar to those for 3-year overall survival (72·5%) that were obtained in the eight cycle R-CHOP14 group of the Ricover-60 study.

Besides efficacy, safety was an important endpoint of our study. The high risk of infectious complications, particularly for opportunistic pathogens, associated with R-CHOP14 has been noted elsewhere.[12–15] In our study, prophylaxis for *Pneumocystis jirovecii* with co-trimoxazole was prescribed. Therefore, we did not record a higher frequency of such infectious complications in the R-CHOP14 group compared with R-CHOP21. Haematological toxic effects were increased slightly in patients assigned R-CHOP14, leading to more red-blood-cell and platelet transfusions in this treatment group than in the R-CHOP21 group. Although we did not note meaningful differences in adverse events, patients allocated R-CHOP14 were admitted for an additional 2 nights compared with individuals assigned R-CHOP21. Finally, as expected from previous work, the number of deaths attributable to treatment was low in both groups.

A major issue of our study was the inability to deliver to an elderly population a dose-dense regimen. In the German Ricover-60 study, the relative dose intensity of chemotherapy delivered to patients was very high, with a median relative dose for myelosuppressive drugs of at least 95% (range 7–111) for eight cycles of R-CHOP14. An early attempt to shorten the interval between two CHOP cycles of chemotherapy in an elderly population[8] saw about 15% of patients receive a relative dose intensity less than 80% for cyclophosphamide and doxorubicin. In our study, about a fifth of patients assigned R-CHOP14 received less than 80% of the planned dose for cyclophosphamide and doxorubicin. Other small series, albeit with different study populations, show similar results.[16] One explanation for our difficulty delivering a dose-dense regimen is the higher proportion of patients with adverse prognostic factors (according to the international prognostic index) in our study than in Ricover-60. Another possibility could be the positive role of the mandatory prephase of treatment in the German study. Adhesion to a treatment schedule outside of clinical trials is known to differ strikingly from that recorded in published studies; in a North American study,[17] 60% of patients older than 60 years, who were treated with CHOP21 with or without rituximab, received a relative dose intensity less than 85% for myelosuppressive drugs.

What is the effect of granulocyte colony-stimulating factor on relative dose intensity? To our knowledge, no trial in elderly patients with aggressive lymphomas receiving CHOP or similar regimens has shown a survival advantage with prophylactic administration of granulocyte colony-stimulating factor.[18,19] In our study, primary prophylaxis with granulocyte colony-stimulating factor was not mandatory but was prescribed at the discretion of the treating doctor. In fact, use of granulocyte colony-stimulating factor was widespread for patients receiving R-CHOP14 and was started as early as the first cycle of treatment, particularly after revised guidelines for use of granulocyte colony-stimulating factor in elderly patients with lymphoma were published.[20] Despite results from two interim analyses, the data and safety monitoring committee recommended no changes to supportive measures. We compared patients who received granulocyte colony-stimulating factor as primary prophylaxis and those who did not receive this treatment during cycle one. Prophylactic prescription of granulocyte colony-stimulating factor had little effect on relative dose intensity for cyclophosphamide (88% *vs* 86%) and doxorubicin (88% *vs* 86%). Furthermore, omission of granulocyte colony-stimulating factor at the first treatment cycle was not associated with decreased progression-free and overall survival in both groups considered separately (data not shown).

By contrast with the period before immunochemotherapy, dose-dense or dose-intense regimens for elderly patients with diffuse large B-cell lymphoma in the rituximab era have never been associated with increased survival. In a study of eight cycles of R-CHOP14 or R-CHOP21 for patients aged 19–88 years with previously untreated diffuse large B-cell lymphoma,[21] the two regimens gave comparable findings for efficacy and toxic effects in all adult age groups, including elderly patients. Together, these data suggest that rituximab combined with chemotherapy has erased the effect of dose-dense chemotherapy. Therefore, other strategies should be investigated, such as use of new agents in combination

with R-CHOP—eg, lenalidomide,[22] bortezomib,[23] or other anti-CD20 agents[24]—or new schedules of administration.[25] In conclusion, in elderly patients with untreated diffuse large B-cell lymphoma, a 2-week dose-dense regimen of R-CHOP does not differ in terms of efficacy from the 3-week standard R-CHOP schedule.

Contributors

A full list of trial investigators is provided in the appendix. RD, HT, NM, GS, TJM, CH, and AB designed the study. RD, HT, NM, GS, CT, SB, HG, MH, CFr, LY, CFe, OC, AVH, AT, AD, OF, CH, and AB collected data. TP and TJM were responsible for pathological review. RD, HT, NM, GS, CH, and AB analysed and interpreted data and wrote the report. All authors had full access to the final version of the report and agreed to submission.

Conflicts of interest

RD has received payment for lectures from Sandoz, Roche, Pfizer, and Celgene; has served as a consultant for Pfizer; has served as a member of a data and safety monitoring committee for a Millennium-Takeda study; and has received travel support from Celgene, Novartis, MundiPharma, and Roche. HT has received payment for lectures from Roche, Celgene, Amgen, and Pfizer; has served as member of an advisory board for Roche and Celgene; has received grants from Celgene and Amgen; and has received travel support from Celgene. NM has served as a member of a data and safety monitoring committee for a Hovon study. GS has received payment for lectures from Roche, Celgene, Amgen, and Mundipharma; has served as member of an advisory board for Roche and Celgene; has served as a consultant for Roche, Gilead, Celgene, and Janssen; and has received travel support from Pfizer, Janssen, and Roche. CT has received payment for lectures from Roche and Sanofi; and has served as a member of an advisory board for Roche and Takeda. LY has received consulting fees from Roche; and has served as a member of an advisory board for Roche. OC has served as a consultant to Roche; has served as a member of an advisory board for Roche, Celgene, and Seattle Genetics; and has received grants from Amgen, Roche, and Chugai. AVH has served as a consultant to Roche. AD has served as a consultant on an advisory board for Roche; has received grant support from Chugai, Roche, and Novartis; has received payment for lectures from Roche, MundiPharma, and Celgene; and has received payment for development of an educational presentation from Roche and MundiPharma. TJM has served as a consultant to Merck. CH has received consulting fees or honoraria from Roche; has received travel support from Amgen; and has served as a consultant on an advisory board for Roche. AB has received payment for lectures from Roche; and has served as a member of an advisory board for Roche. TP, SB, HG, MH, CFr, CFe, AT, and OF declare that they have no conflicts of interest. All authors are members of GELA.

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