Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial

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Summary

Background The outcome of diffuse large B-cell lymphoma has been substantially improved by the addition of the anti-CD20 monoclonal antibody rituximab to chemotherapy regimens. We aimed to assess, in patients aged 18–59 years, the potential survival benefit provided by a dose-intensive immunochemotherapy regimen plus rituximab compared with standard treatment plus rituximab.

Methods We did an open-label randomised trial comparing dose-intensive rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (R-ACVBP) with subsequent consolidation versus standard rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone (R-CHOP). Random assignment was done with a computer-assisted randomisation-allocation sequence with a block size of four. Patients were aged 18–59 years with untreated diffuse large B-cell lymphoma and an age-adjusted international prognostic index equal to 1. Our primary endpoint was event-free survival. Our analyses of efficacy and safety were of the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT00140595.

Findings One patient withdrew consent before treatment and 54 did not complete treatment. After a median follow-up of 44 months, our 3-year estimate of event-free survival was 81% (95% CI 75–86) in the R-ACVBP group and 67% (59–73) in the R-CHOP group (hazard ratio [HR] 0·56, 95% CI 0·38–0·83; p=0·0035). 3-year estimates of progression-free survival (87% [95% CI, 81–91] *vs* 73% [66–79]; HR 0·48 [0·30–0·76]; p=0·0015) and overall survival (92% [87–95] *vs* 84% [77–89]; HR 0·44 [0·28–0·81]; p=0·0071) were also increased in the R-ACVBP group. 82 (42%) of 196 patients in the R-ACVBP group experienced a serious adverse event compared with 28 (15%) of 183 in the R-CHOP group. Grade 3–4 haematological toxic effects were more common in the R-ACVBP group, with a higher proportion of patients experiencing a febrile neutropenic episode (38% [75 of 196] *vs* 9% [16 of 183]).

Interpretation Compared with standard R-CHOP, intensified immunochemotherapy with R-ACVBP significantly improves survival of patients aged 18–59 years with diffuse large B-cell lymphoma with low-intermediate risk according to the International Prognostic Index. Haematological toxic effects of the intensive regimen were raised but manageable.

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Introduction

Diffuse large B-cell lymphoma is the most common haemopoietic malignancy, accounting for 25% of all lymphoid neoplasms.[1] The clinical course of diffuse large B-cell lymphoma has greatly changed over the past 10 years, since the introduction of the chimeric mono-clonal anti-CD20 antibody rituximab for the treatment of patients with lymphoma. A pivotal trial done in 1998 by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) showed that combining rituximab with standard cyclo-phosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy significantly improved response, event-free survival, and overall survival compared with CHOP alone in patients older than 60 years.[2,3] These favourable results have been confirmed by three additional randomised trials in patients both younger and older than 60 years with diffuse large B-cell lymphoma.[4–6] However, despite these significant improvements, some patients are refractory to initial treatment or can relapse after a complete response. In cases where the disease is refractory to immunochemotherapy, the estimate of progression-free survival at 3 years is only 23%, even with subsequent high-dose chemotherapy and autologous stem-cell transplantation.[7] This situation emphasises the importance of first-line treatment when crucial issues are still unresolved, such as establishing the optimum rituximab dose and schedule as well as the optimum chemotherapy regimen to combine with rituximab.

Two randomised studies done in the so-called pre-rituximab era showed that the intensified doxorubicin,

cyclophosphamide, vindesine, bleomycin, and prednisone chemotherapy regimen (ACVBP) with subsequent sequential consolidation, compared with standard CHOP, can improve the outcome both in low-risk[8] and high-risk[9] groups of patients, according to the International Prognostic Index for aggressive lymphoma.[10] Similarly, the Deutsche Studiengruppe Hochmaligne Non-Hodgkin-Lymphome[11] showed that the addition of etoposide to CHOP improves the event-free survival of patients younger than 60 years with aggressive lymphoma. However, in a subsequent study assessing the outcomes of a subgroup of patients receiving CHOP plus etoposide in combination with rituximab compared with those receiving CHOP in combination with rituximab, the advantage conferred by CHOP plus etoposide disappeared, leading to the hypothesis that rituximab could have an equalising effect on differences exhibited by chemotherapy regimens.[5]

To prospectively assess the role of a dose-intensive regimen in combination with rituximab, GELA in 2003 started a multicentre, phase 3, open-label, randomised trial (LNH03-2B), comparing the efficacy and safety of ACVBP plus rituximab (R-ACVBP) versus standard CHOP plus rituximab (R-CHOP) in a selected population of patients aged 18–59 years with diffuse large B-cell lymphoma.

Methods

Participants
Between December, 2003, and December, 2008, in accordance with our protocol, we did a phase 3 multicentre randomised trial in 73 haematology or oncology departments of GELA in France, Belgium, and Switzerland. Patients were eligible if they were aged 18–59 years and had untreated diffuse large B-cell lymphoma that had been diagnosed in accordance with the WHO classification.[12] We required that patients had only one adverse prognostic factor as defined by the age-adjusted International Prognostic Index[10] (raised lactate dehydrogenase, Ann Arbor stage III or IV, or Eastern Cooperative Oncology Group [ECOG] performance status 2–4[13]); a minimum life expectancy of 3 months; and negative HIV, hepatitis B virus, and hepatitis C virus serology tests (except after vaccination). Patients were not eligible if they had T-cell lymphoma; CNS or meningeal involvement by lymphoma; contraindication to any drug included in the chemotherapy regimens; any serious, active disease (according to the investigator's decision); poor renal function (creatinine >150 mmol/L) or poor hepatic function (total bilirubin >30 mmol/L, transaminases >2·5-times the maximum normal level), unless these abnormalities were related to the lymphoma; poor bone-marrow reserve as defined by a neutrophil concentration lower than $1·5 \times 10^9$/L or a platelet concentration lower than 100×10^9/L, unless related to bone-marrow infil-tration; any history of cancer during the past 5 years, with the exception of non-melanoma skin tumours or stage 0 (in situ) cervical carcinoma; treatment with any investigational drug within 30 days before the planned first cycle of chemotherapy and during the study; or any history of treated or untreated indolent lymphoma.

We required patients to provide written informed consent before registration. Our study complied with all provisions of the Declaration of Helsinki and its amendments and was done in accordance with good clinical practice guidelines. Our protocol and informed consent forms were approved by the local and national institutional review boards in each participating centre and country.

Randomisation and masking
Our trial was not masked. We randomly assigned patients in a one-to-one ratio to receive R-ACVBP or R-CHOP. Investigators enrolled the participants, and assignment to treatment was done with a computer-assisted random-isation allocation sequence with a block size of four generated by a statistician centrally at the Groupe d'Etude des Lymphomes de l'Adulte—Recherche Clinique (GELARC) offices with a fax process, without the intervention of the investigators. Treatment allocation was stratified by centre.

Procedures
The extent of the disease was assessed by physical examination; relevant laboratory tests; CT of the chest, abdomen, and pelvis (although MRI was not excluded, only CT was mandated by the protocol); cerebrospinal fluid examination; bone-marrow biopsy; and other investigational procedures, depending on clinical symptoms. The stage of lymphoma was defined in accordance with the Ann Arbor classification. ^{18}F-fluoro-deoxyglucose (^{18}F-FDG) PET was not mandated for staging or assessment of response to treatment. Tumour measurements were assessed by the treating physician or local radiologist. We defined bulky disease as any mass 10 cm or greater at the maximum diameter. Performance status was assessed in accordance with the ECOG scale,[13] and the lactate dehydrogonase level was expressed as the ratio of the maximum value to the normal value.

A central review was done by at least two pathologists from GELA, without knowledge of the patient outcome, to confirm the diagnosis of CD20-positive diffuse large B-cell lymphoma. Tumours were classified in accordance with the WHO classification.[12] Members of the reference pathology panel are listed in the acknowledgments.

Figure 1 shows the protocol outline. Our R-ACVBP regimen consisted of an induction phase of four cycles of R-ACVBP with a subsequent consolidation phase containing different treatment sequences. A cycle of R-ACVBP comprised 375 mg/m² rituximab, 75 mg/m² doxorubicin, and 1200 mg/m² cyclophosphamide on day 1; 2 mg/m² vindesine and 10 mg bleomycin on days 1 and 5; and 60 mg/m² prednisone on days 1–5. Each cycle of R-ACVBP was repeated every 2 weeks. Granulocyte colony-stimulating factor (filgrastim) was also given subcutaneously from day 6 to 13. A sequential consolidation was given 4 weeks after completion of the

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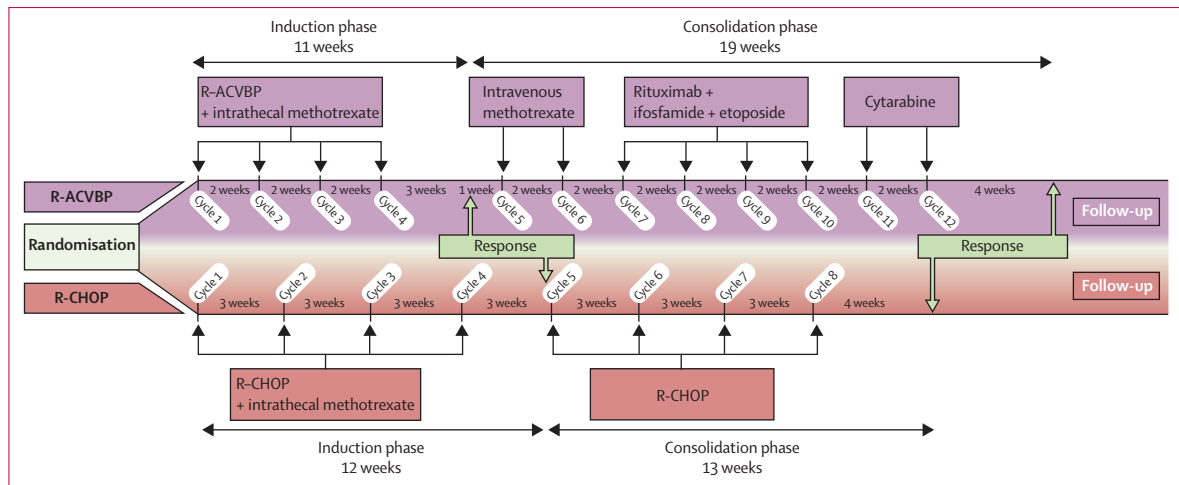herve.tilly@rouen.fnclcc.fr

For the **LNH03-2B protocol** see http://lnh03.gela.org/

Figure 1: Protocol outline
R-ACVBP=rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone. R-CHOP=rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone.

fourth cycle of R-ACVBP, consisting of two cycles of methotrexate (3 g/m²) and calcium folinate rescue, with four subsequent cycles of rituximab (375 mg/m²) combined with etoposide (300 mg/m²) and ifosfamide (1500 mg/m²), and finally two cycles of cytarabine (100 mg/m²) given subcutaneously for 4 days, with each consolidation course being given at 2-week intervals. The R-CHOP regimen consisted of eight cycles repeated at 3-week intervals. Each cycle comprised 375 mg/m² rituximab, 50 mg/m² doxorubicin, 750 mg/m² cyclophosphamide, and 1·4 mg/m² vincristine (up to a maximum dose of 2 mg) on day 1 and 60 mg/m² prednisone on days 1–5. During the first four cycles, the theoretical dose intensity of the R-ACVBP regimen, compared with R-CHOP, increased by a factor of 2·25 for doxorubicin (37·5 mg/m² per week *vs* 16·7 mg/m² per week), 2·4 for cyclophosphamide (600 mg/m² per week *vs* 250 mg/m² per week), and 1·5 for rituximab (187·5 mg/m² per week *vs* 125 mg/m² per week). Patients received 15 mg of intrathecal methotrexate on day 1 of the first four cycles in both study groups for prophylaxis of the CNS. Radiotherapy was not permitted in our protocol.

Tumour responses were assessed by the local investigator after four cycles of R-ACVBP and R-CHOP and at the end of treatment in each group. Responses were classified as complete response, unconfirmed complete response, or partial response. The disease state was identified as stable disease or progressive disease. Responses and disease states were based on the International Workshop 1999 criteria.[14] Follow-up was undertaken by the local investigator. During the first 2 years after treatment, assessment consisted of physical examination and laboratory tests every 3 months, and CT of the chest, abdomen, and pelvis every 6 months. Thereafter, physical examination and laboratory tests were done every 6 months and CT every year.

All adverse events reported by the patient or recorded by the investigator were collected from the case report form in predefined categories. An adverse event was defined as any adverse change from the patient's baseline characteristics, independent of treatment status. Each event was graded according to the National Cancer Institute Common Toxicity Criteria grading system (version 3.0). All grade 3 and 4 events and grade 2 infections were recorded in detail. Grade 1 and 2 adverse events were not extensively described.

Statistical analysis

We used event-free survival, our primary endpoint, to assess sample size. In our previous LNH-98-5 study,[2] we estimated that treatment with R-CHOP conferred a 2-year event-free survival rate of 75% in the population of patients with one factor from the age-adjusted International Prognostic Index. To detect a change in the 2-year event-free survival from 75% to 85% in the R-ACVBP group, we calculated that 380 patients randomly assigned at a ratio of one to one between the two treatment groups, recruited over 4 years, and followed up for a minimum of 1 year, would be needed to achieve 100 events and 80% power at the overall 5% (two-sided) significance level with a log-rank test. We planned an interim analysis on the basis of 40 events after 2 years of inclusion and a follow-up of a minimum of 1 year. We used the O'Brien–Fleming α-spending function to maintain the overall significance level, with α=0·0008 at interim analysis and 0·05 at final analysis. Because our threshold of significance was not met at this interim analysis, we completed the second stage of our trial.

We measured event-free survival from the date of randomisation to the date of the first event. We defined events as death from any cause, disease progression during or after treatment, relapse for complete responders

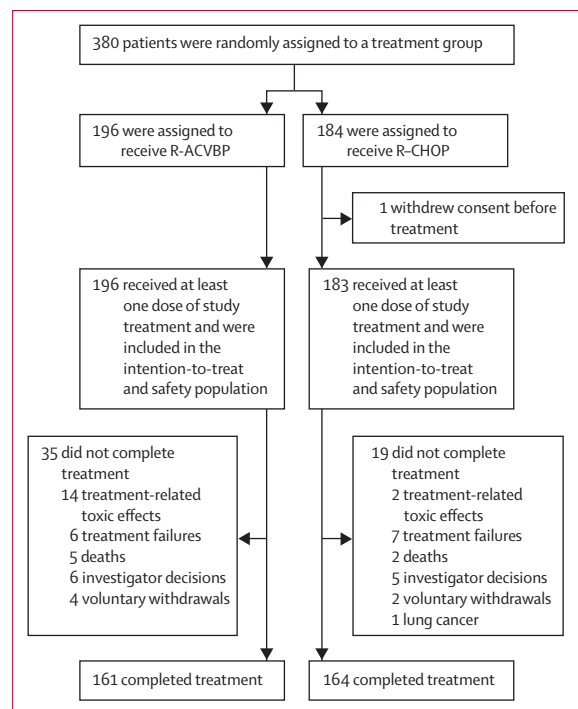|	R-ACVBP group	R-CHOP group
Events for event-free survival	40 (20%)	63 (34%)
Unplanned treatment for lymphoma	15	14
Unplanned chemotherapy	13	10
Unplanned radiotherapy	2	4
Progression or relapse	19	43
Death	6	6
Events for progression-free survival	28 (14%)	51 (28%)
Progression of relapse	21	44
Death	7	7
Events for overall survival	15 (8%)	31 (17%)
Lymphoma*	8	22
Unrelated to lymphoma progression during treatment	5	3
Unrelated to lymphoma progression after treatment		
Second cancer	..	2
Cardiac cause	1	..
Pneumonitis	..	2
Gastric haemorrhage	..	1
Suicide	..	1
Unknown	1	..

Data are n (%) unless otherwise stated. R-ACVBP=rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone. R-CHOP=rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone. *Deaths from lymphoma progression or related to treatment of relapse or progression.

Table 2: Analysis of endpoints in the intention-to-treat population

planned dose intensity as total planned cumulative dose received during the first 4 cycles divided by the theoretical time elapsed between the first and fourth cycles (56 days for R-ACVBP and 84 for R-CHOP).

Our analyses of efficacy and safety were of the intention-to-treat population. One patient who withdrew consent before any procedure was excluded from this population. All p values are two-sided. Statistical analyses were done with SAS 9.1.3 software by the investigators of the GELARC statistical office. This study is registered with ClinicalTrials.gov, number NCT00140595.

Role of the funding source

GELA, via GELARC, was involved in the random assignment procedure, distribution and collection of case report forms, data entry and validation, coordination of monitoring procedures, elaboration and mailing of queries, reporting of serious adverse events, coordination of histological review, relation with investigators, transmission of enrolment status to the sponsor, statistical analysis, and production of 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

Figure 2 shows the trial profile. We enrolled 380 patients into our trial, of which 379 received at least one dose of the protocol-planned treatment. The main characteristics of our patients were similar in the two groups (table 1). The main criteria providing an age-adjusted International Prognostic Index score of 1 were raised lactate dehydrogenase concentration and Ann Arbor stage III–IV in 44% and 55% of patients, respectively. 21 patients had an age-adjusted International Prognostic Index score other than 1 (table 1). Central pathological review was completed for 344 patients (91%), with diffuse large B-cell lymphoma confirmed in 90% of the R-ACVBP group and 94% of the R-CHOP group. At the data-cutoff point, Jan 1, 2010, the median follow-up was 44 months (IQR 27–53).

54 patients did not complete either treatment regimen (figure 2). 190 patients (97%) in the R-ACVBP group received the first four cycles of the planned treatment and 177 (97%) in the R-CHOP group. The median interval between these cycles was 14 days (range 12–57, IQR 14–17) in the R-ACVBP group and 21 days (14–62, 21–21) in the R-CHOP group. Based on data collected from the population who received the first four cycles of each treatment, the received dose intensities for doxorubicin were 92·1%, for cyclophosphamide were 93·0%, and for rituximab were 92·3% of the planned dose for R-ACVBP, and 98·4%, 98·6%, and 98·6% for R-CHOP, respectively.

Fewer events were recorded in the R-ACVBP group than the R-CHOP group (table 2, figure 3). Event-free survival was significantly longer for patients treated with R-ACVBP than for those treated with R-CHOP (p=0·0035), with 3-year estimates of 81% (95% CI 75–86) for R-ACVBP and 67% (59–73) for R-CHOP. The HR of the R-ACVBP group for event-free survival shows that this regimen reduced the risk of experiencing an event by 44% compared with R-CHOP in this population (figure 3). Progression-free survival was significantly longer in the R-ACVBP group, resulting in a 3-year progression-free survival of 87% (81–91) with R-ACVBP and 73% (66–79) with R-CHOP (p=0·0015; figure 3).

The overall response rate was 90% in the R-ACVBP group and 87% in the R-CHOP group (p=0·47; table 3). A complete response or unconfirmed complete response was achieved in 162 patients (83%) in the R-ACVBP group and 146 (80%) in the R-CHOP group (p=0·46). In complete responders, the disease-free survival was significantly longer in the R-ACVBP group, with a 3-year estimate of 91% (95% CI 85–95) compared with 80% (73–86) in the R-CHOP group (p=0·0019; figure 3). 15 patients in the R-ACVBP group and 33 in the R-CHOP group experienced a relapse. There was no CNS relapse in the R-ACVBP group but two in the R-CHOP group. There were fewer deaths in the R-ACVBP group than the R-CHOP group (table 2). Overall survival differed significantly, with a 3-year estimate of 92% (87–95) in the R-ACVBP group and 84% (77–89) in the R-CHOP group (p=0·0071; figure 3).

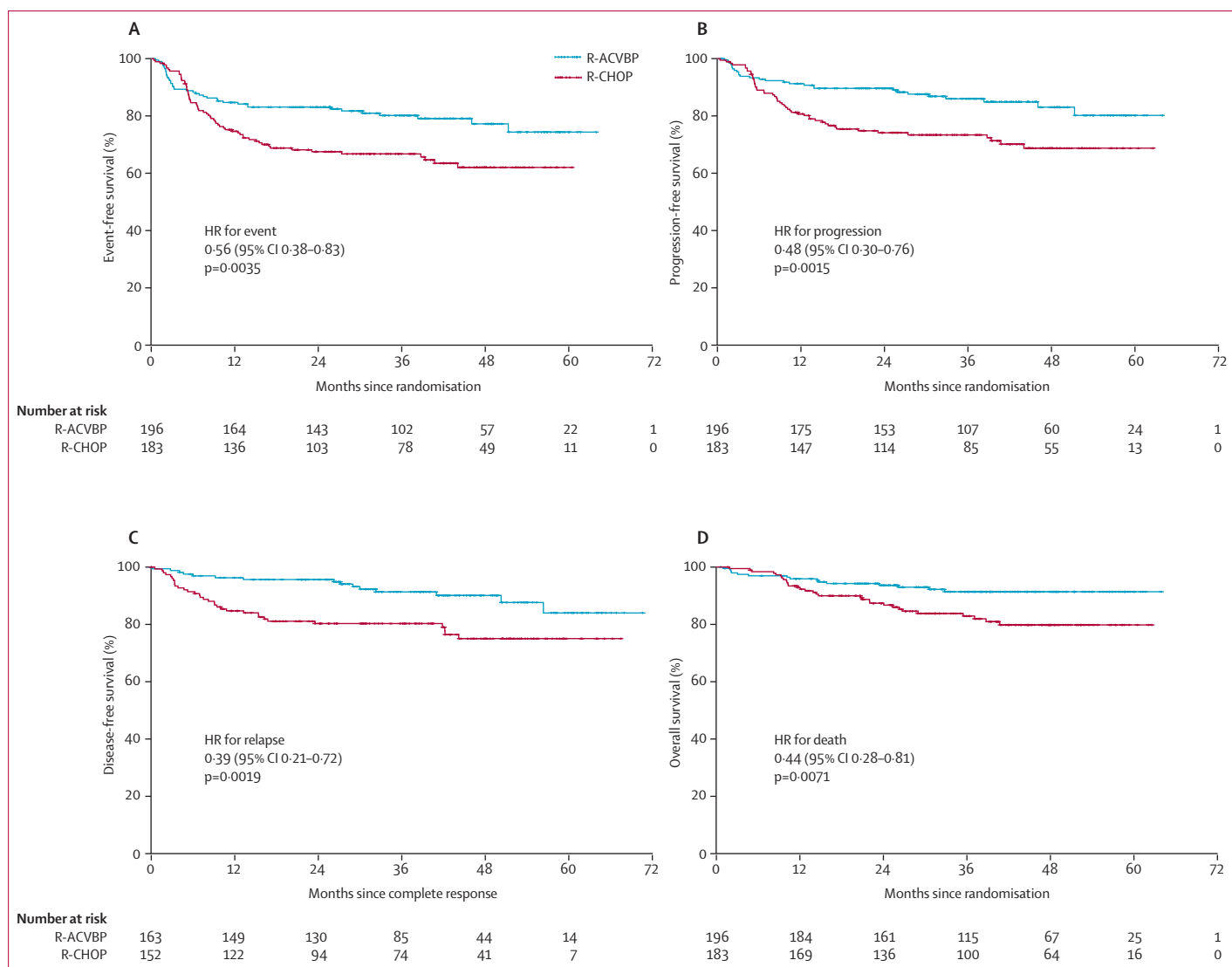Per-protocol analyses of patients who met all eligibility criteria, who had confirmed diffuse large B-cell lymphoma

Figure 3: **Kaplan-Meier estimates of outcomes by treatment group**
Event-free survival for the 379 patients in the intention-to-treat population (A). Progression-free survival for the 379 patients in the intention-to-treat population (B). Disease-free survival for the 315 patients who achieved complete or unconfirmed complete response to treatment (C); the number of patients in these estimates is different from the number of patients in complete or unconfirmed complete remission at the end of treatment because disease-free survival is calculated from the initial recorded response. Overall survival for the 379 patients in the intention-to-treat population (D). R-ACVBP=rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone. R-CHOP=rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone. HR=hazard ratio.

at histology review, and who received at least four cycles of the allocated treatment (165 patients in the R-ACVBP group and 156 patients in the R-CHOP group) confirmed the results of our intention-to-treat analyses: event-free survival (p=0·0027), progression-free survival (p=0·0011), and overall survival (p=0·0023).

The presence of a bulky mass was the only factor identified as unfavourable for overall survival (HR 0·40, 95% CI 0·22–0·72) but not for progression-free survival (0·72, 0·44–1·19). 3-year progression-free survival of patients with bulky disease was 77% (95% CI 58–88) in the R-ACVBP group and 73% (58–84) in the R-CHOP group (HR 0·69; p=0·40), and for patients without any

mass larger than 10 cm diameter was 89% (83–93) in the R-ACVBP group and 73% (65–85) in the R-CHOP group (HR 0·43; p=0·0017). Interactions between any baseline factor and treatment group were not significant.

The most common adverse events were haematological toxic effects in both groups (table 4). Patients receiving R-ACVBP had higher incidences of anaemia, thrombocytopenia, neutropenia, and febrile neutropenia, which were also more commonly grade 3 or 4, than the R-CHOP group. Recorded infections during neutropenic periods were also more common in the R-ACVBP group. Grade 3 or 4 mucositis was another adverse event associated with the R-ACVBP regimen and not recorded for the R-CHOP

	R-ACVBP group (n=196)	R-CHOP group (n=183)
Complete response	114 (58%)	96 (52%)
Unconfirmed complete response	48 (24%)	50 (27%)
Partial response	14 (7%)	14 (8%)
Stable disease	4 (2%)	1 (1%)
Progressive disease	7 (4%)	17 (9%)
Death	5 (3%)	3 (2%)
Not assessed	4 (2%)	2 (1%)

Data are n (%). R-ACVBP=rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone. R-CHOP=rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone. Response to treatment was assessed in accordance with the International Workshop 1999 criteria.[14]

Table 3: Response to treatment by treatment group

	Any grade		Grade 3 or greater	
	R-ACVBP group	R-CHOP group	R-ACVBP group	R-CHOP group
Anaemia	194 (99%)	138 (75%)	68 (35%)	10 (5%)
Neutropenia	189 (86%)	157 (83%)	153 (78%)	118 (64%)
Thrombocytopenia	151 (77%)	56 (31%)	59 (30%)	6 (3%)
Febrile neutropenia	77 (39%)	16 (9%)	75 (38%)	16 (9%)
Infection in neutropenic period	34 (17%)	12 (7%)	26 (13%)	7 (4%)
Infection out of neutropenic period	32 (16%)	19 (10%)	9 (5%)	5 (3%)
Mucositis	106 (54%)	25 (14%)	35 (18%)	0
Nausea or vomiting	69 (35%)	56 (31%)	6 (3%)	4 (2%)
Diarrhoea	31 (16%)	16 (9%)	1 (1%)	1 (1%)
Cardiac-related toxic effects	5 (3%)	1 (1%)	0	1 (1%)
Aminotransferase elevation	58 (30%)	50 (27%)	4 (2%)	4 (2%)
Creatinine elevation	11 (6%)	8 (4%)	1 (1%)	0
Lung-related toxic effects	33 (17%)	15 (8%)	2 (1%)	2 (1%)
Neurological toxic effects	50 (30%)	46 (25%)	11 (6%)	4 (2%)
Vascular toxic effects	21 (11%)	5 (3%)	13 (7%)	2 (1%)
Rash	51 (26%)	19 (10%)	3 (2%)	0
Other toxic effects	130 (66%)	118 (64%)	25 (13%)	14 (8%)

Data are the number and proportion of patients with an event in at least one cycle. Toxic-effect grades are based on the National Cancer Institute Common Terminology Criteria (version 3.0).[15]

Table 4: Toxic effects by treatment group

group. At least one red-blood-cell transfusion was done in 99 (51%) of 196 patients in the R-ACVBP group and 13 (7%) of 183 in the R-CHOP group; platelet transfusions were also done in 25 (13%) of 196 and one (1%) of 183, respectively. Adverse events that were judged serious were more common in the R-ACVBP group (82 [42%] of 196 patients) than in the R-CHOP group (28 [15%] of 183). There were five deaths unrelated to lymphoma progression during the treatment period in the R-ACVBP group (three sepsis, one unknown cause, and one intrathecal vindesine injection) and three in the R-CHOP group (two sepsis and one unknown cause). At the time of our analysis, one malignancy had been recorded for the R-ACVBP group (lung cancer) and two for the R-CHOP group (biliary duct and lung cancer).

Discussion

After more than 3 years of follow-up, all our study endpoints were met, with significant improvements of event-free, progression-free, disease-free, and overall survival in patients treated with R-ACVBP.

The introduction of rituximab in association with CHOP chemotherapy has substantially improved the outcome of patients with diffuse large B-cell lymphoma. However, the results of the R-CHOP regimen, which has been widely thought the standard of care, remains suboptimum in the treatment of younger patients. In recent years, several phase 2 trials have shown promising results regarding the association of intensive chemotherapy and rituximab.[16–19] Most of these regimens were proposed for patients with high-risk disease and contained an intensive chemotherapy schedule with stem-cell support.[16–18] By contrast, dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) is an intensified regimen where pharmacodynamic dosing is on the basis of neutrophil nadir.[19] A phase 2 study of dose-adjusted EPOCH plus rituximab showed promising outcomes in low and intermediate International Prognostic Index groups with progression-free survival similar to that of R-ACVBP.

ACVBP has been used in Europe to treat patients with aggressive lymphoma for the past 30 years.[20,21] The regimen consists of two different phases. The first part is an induction phase of four cycles with higher doxorubicin and cyclophosphamide doses, given at a shortened interval. During the second phase, patients receive a sequential consolidation treatment with drugs not used during induction. ACVBP improves results over CHOP in comparative trials assessing patients with localised diffuse large B-cell lymphoma[8] and patients with more advanced disease.[9] The association of rituximab with ACVBP in patients younger than 60 years with an age-adjusted International Prognostic Index score of 1, as in our trial, seems to improve progression-free survival from 81% at 2 years[22] to 90%.

The lower rate of disease progression during the treatment phase and fewer relapses in patients who reached a complete response accounted for the prolonged progression-free survival and overall survival in our R-ACVBP group. However, we do not know which phase of the R-ACVBP regimen improves the outcome. A trial is ongoing that aims to assess the quality of remission after R-ACVBP and R-CHOP by comparing ^{18}F-FDG PET after two and four induction cycles.[23] The role of consolidation is probably important. High-dose methotrexate plus calcium folinate rescue is associated with a low risk of CNS relapse in diffuse large B-cell lymphoma.[24] Ifosfamide, etoposide, and cytarabine, contained in the consolidation, are the most common drugs used in salvage regimens after relapse subsequent to anthracycline-based treatment.[7]

Outcome data in our patients treated with standard R-CHOP are consistent with our initial hypothesis

(panel),[2] but the 3-year event-free survival 67% (59–73) seems to be in the lower range of the equivalent population of the MabThera International Trial:[5] 74% (66–84) for bulk disease or 76% (67–86) for no bulk disease. In the MabThera International Trial, various chemotherapy regimens plus rituximab did not produce major differences in outcome. However, 40% of the patients treated with the rituximab combination received radiotherapy. Whether radiotherapy could affect the outcome in this population treated with R-CHOP is being studied at present by the Deutsche Studiengruppe fur Hochmaligne Non-Hodgkin-Lymphome (registered with ClinicalTrials.gov, number NCT00278408).

The profile of toxic effects for the R-ACVBP regimen is well characterised. The induction phase is associated with noticeable haematological toxic effects, which is why the regimen is only used in patients younger than 60 years.[9] Most patients experience substantial neutropenia between day 9 and day 13 of each cycle, with a substantial proportion (39%) having a febrile episode despite the use of growth factor. However, our trial and previous ones involving the ACVBP regimen[25] have shown that life-threatening complications related to treatment are uncommon in a population of patients younger than 60 years with good performance status. The care of many patients included in our trial has been managed in the oncology departments of community hospitals of the 73 participating centres from the GELA network. Although ACVBP is an intensified regimen, the total dose of doxorubicin and cyclophosphamide given is less than the dose received during eight cycles of CHOP. This dose might account for the somewhat low incidence of secondary malignancies and cardiac-related toxic effects recorded in a large cohort of 2837 ACVBP-treated patients that were followed up over a median of 74 months.[26] We plan to do long-term follow-up of our patient cohort.

In the context of chemotherapy, interactions between the microenvironment and cancer cells, especially lymphoma cells, are complex.[27] There is some evidence that antibody-dependent cellular cytotoxicity mediated by activation of natural-killer cells contributes to the clinical response to rituximab.[28] Investigators have postulated that intensive chemotherapy could compromise the efficacy of rituximab by impairing immune cellular mechanisms.[5] However, the results of our study do not favour such a hypothesis.

Modifications of immunochemotherapy regimens are still worthwhile and are being assessed at present. In our selected population, we did not identify any factor to suggest that a specific patient category would benefit from treatment over the other. The favourable results obtained with R-ACVBP front-line regimen should be further assessed in view of the biological heterogeneity of diffuse large B-cell lymphoma,[29] to assess whether some patients with specific subtypes are more to likely to benefit from this intensive therapy, as it has been suggested for dose-adjusted EPOCH plus rituximab,[19] whereas R-CHOP

Panel: Research in context

Systematic review

We searched Medline from January, 2002, to May, 2011, for full papers reporting randomised clinical trials with the terms "rituximab" and "diffuse large B-cell lymphoma". We identified four randomised clinical trials comparing an association of chemotherapy and rituximab versus chemotherapy alone in patients given first-line treatment for diffuse large B-cell lymphoma.[2,4–6] Only one of these trials has been done in patients younger than 60 years.[5] We did not identify any clinical trial that compared two chemotherapy regimens combined with rituximab.

Interpretation

These studies have established the addition of the anti-CD20 monoclonal antibody rituximab with a chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) as a new standard of care. However, CHOP plus rituximab is suboptimum for a substantial number of patients who could relapse and are not salvaged by subsequent therapies. Our results show that rituximab combined to the intensified multidrug regimen of doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP), as first-line treatment, improves the survival of young patients with low-intermediate-risk diffuse large B-cell lymphoma. Haematological and mucosal toxic effects induced by ACVBP plus rituximab are raised but manageable in a multicentre setting.

might be sufficient for others. The possibility of decreasing the intensity of immunochemotherapy could also be explored in selected patients who show a rapid response to treatment, assessed with interim PET. Pending these results and the advent of new targeted therapies in front-line treatment, intensified immunochemotherapy with R-ACVBP represents an alternative to R-CHOP to improve survival in patients younger than 60 years with diffuse large B-cell lymphoma of low-intermediate risk.

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Conflicts of interest

Acknowledgments

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