Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial

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Summary

Background **Diffuse large B-cell lymphoma is a common cancer in elderly patients. Although treatment has been standardised in younger patients, no prospective study has been done in patients over 80 years old. We aimed to investigate the efficacy and safety of a decreased dose of CHOP (doxorubicin, cyclophosphamide, vincristine, and prednisone) chemotherapy with a conventional dose of rituximab in elderly patients with diffuse large B-cell lymphoma.**

Methods **We did a prospective, multicentre, single-arm, phase 2 study of patients aged over 80 years who had diffuse large B-cell lymphoma. Patients were included from 38 centres in France and Belgium. All patients received six cycles of rituximab combined with low-dose CHOP (R-miniCHOP) at 3-week intervals. Patients received 375 mg/m² rituximab, 400 mg/m² cyclophosphamide, 25 mg/m² doxorubicin, and 1 mg vincristine on day 1 of each cycle, and 40 mg/m² prednisone on days 1–5. The primary endpoint was overall survival, both unadjusted and adjusted for treatment and baseline prognostic factors. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, NCT01087424.**

Findings **150 patients were enrolled between Jan 9, 2006, and Jan 23, 2009 and 149 were included in the intention-to-treat analyses. Median age was 83 years (range 80–95). After a median follow-up of 20 months (range 0–45), the median overall survival was 29 months (95% CI 21 to upper limit not reached); 2-year overall survival was 59% (49–67%). In multivariate analyses, overall survival was only affected by a serum albumin concentration of 35 g/L or less (hazard ratio 3·2, 95% CI 1·4–7·1; p=0·0053). Median progression-free survival was 21 months (95% CI 13 to upper limit not reached), with a 2-year progression free survival of 47% (38–56). 58 deaths were reported, 33 of which were secondary to lymphoma progression. 12 deaths were attributed to toxicity of the treatment. The most frequent side-effect was haematological toxicity (grade ≥3 neutropenia in 59 patients; febrile neutropenia in 11 patients).**

Interpretation **R-miniCHOP offers a good compromise between efficacy and safety in patients aged over 80 years old. R-miniCHOP should be considered as the new standard treatment in this subgroup of patients.**

Funding **Groupe d'Etude des Lymphomes de l'Adulte (GELA).**

Published Online
April 8, 2011
DOI:10.1016/S1470-2045(11)70069-9

See Online/Comment
DOI:10.1016/S1470-2045(11)70080-8

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Introduction

Diffuse large B-cell lymphoma is the most common lymphoid malignancy worldwide.[1] Its incidence steadily increases with age and about 40% of cases occur in patients aged over 70 years.[1,2] However, few prospective data are available on the outcome of patients aged over 80 years. Retrospective analyses have shown that the outcome of elderly patients is worse than that of younger patients but that some elderly patients do have a complete response to treatment and long-term survival.[3–6]

Whether diffuse large B-cell lymphomas in the elderly differ intrinsically from those in younger patients is not clear. Although there is no specific histological characteristic or genetic abnormality of diffuse large B-cell lymphoma in elderly people, the distribution of gene-expression profile subtypes with distinct prognosis might differ with age.[7] Lymphoma in elderly patients is not substantially less responsive to treatment than in younger patients, and the main reason for the poor outcome of very old patients is their decreased ability to tolerate treatment.[8] Impaired bone-marrow function, altered drug metabolism, and presence of comorbid diseases can increase the number of treatment-related complications. Several attempts to decrease doses of the standard chemotherapy regimen CHOP (doxorubicin, cyclophosphamide, vincristine, and prednisone) or to substitute less toxic drugs in the combination have decreased toxicity but did not improve survival.[9–11]

Over the past 10 years, since the introduction of the chimeric anti-CD20 monoclonal antibody rituximab as the standard treatment, the treatment outcome of patients with diffuse large B-cell lymphoma has changed dramatically. In a randomised open-label trial by the Groupe d'Etudes des Lymphomes de l'Adulte (GELA) in patients aged 60–80 years, the association of CHOP and rituximab was significantly superior to CHOP alone in

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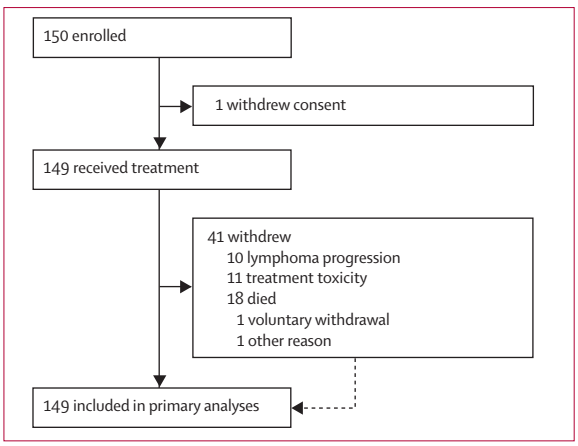

Figure 1: **Trial profile**

terms of complete response rate and survival, without a clinically significant increase in toxicity.[12–14] This study did not include patients aged over 80 years but did show a similar benefit for patients aged 60–70 years, 71–75 years, and 76–80 years.[13] These results have since been replicated by two randomised trials in a similar patient population,[15,16] but no prospective study of this association has been done for patients aged over 80 years.

After the results of a small retrospective study[6] that showed that rituximab could help maintain efficacy of a dose-reduced regimen in patients over 80 years old who had non-Hodgkin lymphoma, we decided to assess the efficacy and safety of the combination of a standard dose of rituximab and an attenuated dose of chemotherapy in this patient population.

Methods

Study design and patients

For the **trial protocol** see http://lnh03-7b.gela.org/studydoc/14_ETUDE/protoversionfinale.pdf

We did a prospective, multicentre, single-arm study of a low-dose CHOP chemotherapy regimen and rituximab (R-miniCHOP) in elderly patients with diffuse large B-cell lymphoma. GELA ran the study in 38 centres in France and Belgium. Patients were eligible if they were aged over 80 years and had untreated histologically proven CD20+ diffuse large B-cell lymphoma according to WHO classification.[17] Inclusion criteria were Ann Arbor stage I bulky to stage IV disease; age-adjusted international prognostic index (IPI)[18] score of 1, 2, or 3 (based on disease stage, performance status, and lactate dehydrogenase concentration; a score of 2–3 suggests a higher risk of death than a score of 0–1); Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less;[19] minimum life expectancy of 3 months; and negative HIV, hepatitis B virus, and hepatitis C virus serology test 4 weeks or less before enrolment (except after vaccination).

Exclusion criteria were any other lymphoma subtype; history of treated or non-treated indolent lymphoma; CNS or meningeal involvement; contraindication to any drug in the chemotherapy regimen; serious active disease according to the investigator's decision; poor renal function, defined as creatinine concentration greater than 150 µmol/L; poor hepatic function, defined as total bilirubin concentration greater than 30 µmol/L or transaminases over 2·5 times the maximum normal concentration, unless these abnormalities were related to the lymphoma; poor bone-marrow reserve, defined as neutrophil count less than $1·5\times10^9$/L or platelet count less than 100×10^9/L, unless caused by bone-marrow infiltration; 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; or under care of a guardian.

Patients signed written informed consent before enrolment. The study was approved by an independent research ethics committee and was done in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines, the Declaration of Helsinki (1996), and applicable local regulatory requirements and laws.

Procedures

Patients received six cycles of R-miniCHOP administered at 3-week intervals. R-miniCHOP consisted of 375 mg/m² rituximab (Hoffmann-La Roche, Basel, Switzerland), 25 mg/m² doxorubicin (Sandoz SAS, Levallois-Perret, France), 400 mg/m² cyclophosphamide (Baxter, Deerfield, IL, USA), and 1 mg vincristine (Teva, La Defense, France) on day 1 of each cycle; and 40 mg/m² oral prednisone (Sandoz, Levallois-Perret Cedex, France) on days 1–5. Prevention of tumour lysis syndrome by alkalinisation or hypouricaemic drugs was done if necessary. Antiemetic therapy with SHT3 antagonists was given at each cycle. Prophylactic granulocyte colony-stimulating factor (G-CSF) or erythropoietin support was left to the discretion of the treating physician. However, in the event of severe neutropenia or neutropenic fever, subcutaneous G-CSF was recommended from day 6 to 13 of the subsequent cycle or until neutrophils were $1·0\times10^9$/L or more. There was no dose adjustment in the event of haematological toxicity. However, the next R-miniCHOP cycle was postponed until the neutrophil count reached $1·0\times10^9$/L and the platelet count 100×10^9/L, with a maximum of 28 days between two consecutive cycles. If these counts were not reached within 28 days, treatment was stopped. In the event of grade 2 neurological vincristine-related toxicity (sensory or motor polyneuritis, constipation, or visual or auditory changes) vincristine was discontinued. Relative dose intensity for doxorubicin and cyclophosphamide was calculated for patients who received the six planned cycles as the ratio of received dose intensity to theoretical dose intensity, as previously described by Hryniuk.[20]

The following assessments were done by the treating physician within 1 month before the first treatment cycle:

	Patients (n=149)
Men	51 (34%)
Age (years)	83 (80–95)
Performance status	
0	27 (18%)
1	72 (48%)
2	50 (34%)
Ann Arbor stage	
I	13 (9%)
II	24 (16%)
III	35 (23%)
IV	77 (52%)
Tumour mass ≥10 cm	30 (20%)
>1 extranodal sites	55 (37%)
LDH concentration >618 U/L	102 (68%)
B symptoms*	49 (33%)
β2-microglobulin ≥3 mg/L	82/112 (73%)
Serum albumin <35 g/L	69/137 (50%)
IPI	
0–1	13 (9%)
2	31 (21%)
3	46 (31%)
4–5	59 (40%)
Age-adjusted IPI	
0	15 (10%)
1	36 (24%)
2	66 (44%)
3	32 (21%)
IADL scale†	
Without limitation (score 4)	63 (47%)
With limitation (score <4)	72 (53%)

Data are number (%) or median (range). LDH=lactate dehydrogenase. IPI=international prognostic index. IADL=instrumental activities of daily living. Percentages do not add up to 100% in some cases because of rounding. *fever, night sweats, and weight loss. †Completed by 135 patients.

***Table 1*: Patient characteristics**

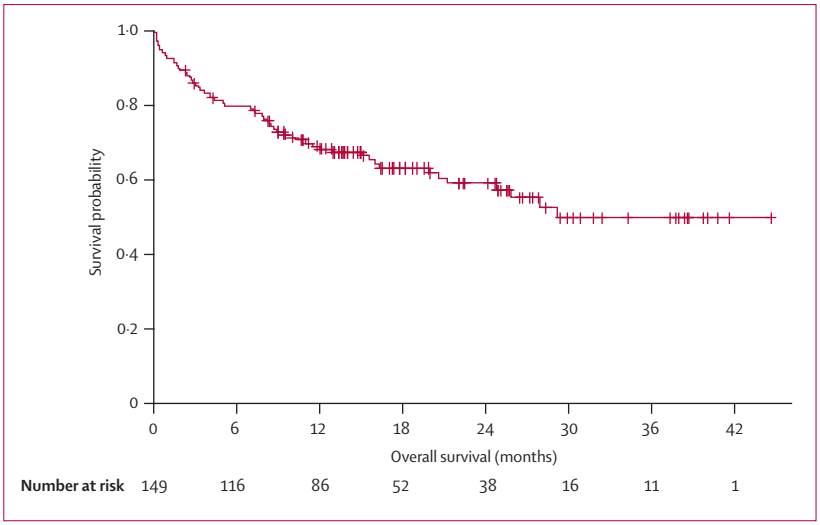

***Figure 2*: Overall survival**

full history, physical examination, instrumental activities of daily living (IADL) scale,[21,22] thoracic and abdominal computerised scan, electrocardiogram, and assessment of resting ejection fraction by echocardiography or an isotopic method. Cerebrospinal fluid examination, bone-marrow biopsy, and pulmonary function assessment was not mandatory. ^{18}Fluorodeoxyglucose PET was also not mandatory for staging or for assessment of response.

Laboratory assessments were done by the treating physician within 1 week before first chemotherapy and included lactate dehydrogenase, β2-microglobulin, serum creatinine, transaminase, bilirubin, alkaline phosphatase, and C-reactive protein concentrations; serum electrophoresis; and complete blood cell counts. HIV, hepatitis B virus, and hepatitis C virus serology was done 4 weeks or less before treatment. IADL consisted of a simple questionnaire that included the following items: ability to use a telephone, shopping, medication use, and ability to handle finance. The sum score of all four items was calculated and patients were classified as being without limitation in the event of a full sum score (4) and with limitation in the event of a sum score less than 4.[21,22] Quality of life assessment was not planned in the protocol. Tumour measurements were assessed by the treating physician or local radiologist, and bulky disease was defined as any mass with a maximum diameter of 10 cm or more. Performance status was assessed with the ECOG scale.[19] Lactate dehydrogenase concentration was expressed as the ratio of the maximum value to the normal upper value. A central review was done by at least two pathologists from the GELA who were masked to patient outcome. In case of discrepancy, a third opinion was requested to reach a consensus.

Tumour responses were assessed by the treating physician after three cycles of R-miniCHOP and at the end of treatment. Responses were classified as complete response, unconfirmed complete response, partial response, stable disease, or progressive disease according to the clinical and radiological criteria of the international workshop.[23] Follow-up was done by the local investigator every 3 months for the first 2 years after treatment and every 6 months thereafter. Follow-up is ongoing.

The primary endpoint was overall survival, both unadjusted and adjusted for treatment and baseline prognostic factors. Secondary endpoints were response to treatment; event-free survival (events defined as death from any cause, relapse for complete responders and undocumented complete responders, progression during or after treatment, and changes of therapy during treatment); disease-free survival for complete responders and unconfirmed complete responders; progression-free survival; and safety. We measured overall survival from the date of inclusion to date of death, irrespective of cause. Patients who were alive at the time of analysis

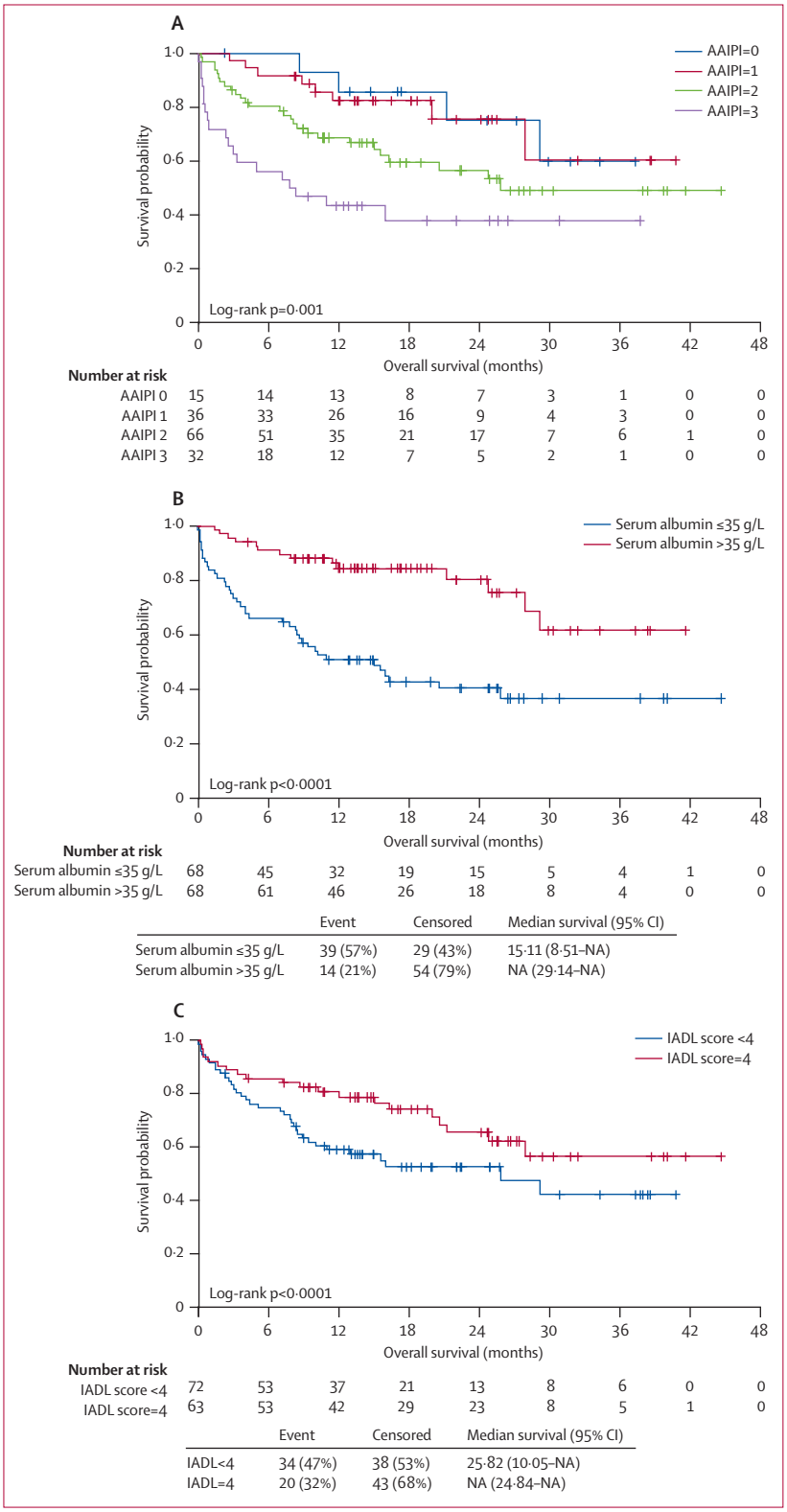

***Figure 3*: Overall survival according to various criteria**
According to (A) age-adjusted international prognostic index, (B) serum albumin concentration at the time of diagnosis, and (C) instrumental activities of daily living scale. AAIPI=age-adjusted international prognostic index. NA=not applicable. IADL=instrumental activities of daily living.

were censored at the most recent date when they were known to be alive or at the stopping date if the most recent date was later. Progression-free survival was measured from date of inclusion to date of progression, relapse, or death from any cause and disease-free survival from the time of attainment of a complete response, unconfirmed complete response to disease recurrence, or death as a result of lymphoma or toxicity of treatment.

All adverse events reported by the patient and witnessed by the investigator were collected from case-report forms in predefined categories. Case-report forms were completed on a regular basis. An adverse event was defined as any adverse change from the patient's baseline condition, whether or not it was deemed related to the treatment. 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 thoroughly described.

Statistical analysis

With a one-arm survival sample size, we calculated the sample size on the basis of a comparison to a fixed reference level. From our previous studies that included patients older than 80 years who had a performance status of 0–2, we estimated a 2-year survival rate of 25%. To detect a change in the 2-year overall survival of 15% in patients treated by R-miniCHOP who had a performance status of 0–2 and IADL score greater than 2, we needed 75 patients to be recruited over 3 years and followed up for a minimum of 1 year (80% power at a 5% significance level, two-sided). We estimated that 50% of patients older than 80 years who had a performance status of 0–2 would have an IADL score greater than 2. This led to a total sample size of 150 patients.

We did efficacy analyses in the intention-to-treat population. We summarised quantitative variables in tables displaying sample size, mean, standard deviation, median, and range. Qualitative variables were described in terms of numbers of each response category, which were converted into percentages of the number of patients or adverse events examined, depending on the unit under investigation. Censored data were presented as Kaplan-Meier plots of time to first event and summaries of Kaplan-Meier estimates for criterion rates at fixed time points, with a 95% CI. We calculated the median time to event (if reached) with 95% CI. Estimates of prognostic factors were expressed as hazard ratios and 95% CI based on the Cox regression. We did two-sided statistical tests, with a 5% level of significance. Survival endpoints were analysed with the log-rank test. We used Cox model regression to assess the effect of prognostic factors on overall survival in multivariate analyses. All statistical analyses were done in SAS (version 9.1.3) by

the investigators of the GELA-Recherche Clinique (GELA-RC) statistical office.

This study is registered with ClinicalTrials.gov, NCT01087424.

Role of the funding source

The study was designed by the GELA scientific committee and was finalised in consultation with all investigators. All logistical aspects of this study were managed by GELA-RC. Data were collected by GELA-RC and analysed by GELA-RC and the corresponding author. The corresponding author was also responsible for data interpretation and writing of the report. All authors had full access to the data in the study and the corresponding author had final responsibility for the decision to submit the manuscript for publication.

Results

From Jan 9, 2006, to Jan 23, 2009, 150 patients (51 men and 99 women) were enrolled in the study, 149 of whom received treatment and were included in the intention-to-treat analyses (figure 1). The imbalance between men and women is consistent with the demographic distribution of elderly men and women. Table 1 shows patient characteristics. All patients had a performance status score lower than or equal to 2, according to the protocol criteria. 75% of patients had an Ann Arbor stage III or IV, and lactate dehydrogenase concentration was higher than normal in 68% of patients. Age-adjusted IPI was 2–3 in 66% of patients. 135 patients completed the IADL questionnaire, 47% of whom were in the without limitation group. 69 of 149 patients had bone marrow biopsy; the biopsy was involved in 13. Central pathological review was completed for 141 of 149 patients; diffuse large B-cell lymphoma was reported in 132 of these patients, mantle cell lymphoma in three patients, lymphocytic lymphoma and angioimmunoblastic lymphoma in one patient each, and unclassifiable B-cell lymphoma in four patients. At the data cutoff point (Oct 1, 2009, when more than 90% of patients had completed follow-up), median follow-up was 20 months (range 0–45). Four centres of the GELA network included more than ten patients, six centres included between five and nine patients, and 28 centres included less than five patients.

Of the 149 patients in the intention-to-treat population, 108 completed the six cycles of the treatment regimen. Median interval between cycles was 21 days (range 14–56; one patient had a protocol violation and restarted chemotherapy after 56 days). Relative median dose intensity for the 108 patients who completed all treatment cycles was 97% for both doxorubicin (range 64–106) and cyclophosphamide (66–358).

Median overall survival was 29 months (95% CI 21 to upper limit not reached; the 2-year overall survival rate was 59% (95% CI 49–67; figure 2). In univariate analyses, poor performance status, age-adjusted IPI score of 2–3, number of extra-nodal sites greater than 1, serum albumin 35 g/L or less, tumour mass greater than 10 cm, and IADL score less than 4 seemed to be predictive of shorter survival (figure 3, table 2). Survival did not seem to be associated with centre sample size (data not shown). In multivariate analyses that included these variables, survival was only affected by a serum albumin level 35 g/L or less (hazard ratio 3·2, 95% CI 1·4–7·1; p=0·0053; table 3).

58 deaths were reported during treatment and follow-up (webappendix p 2), 33 of which were secondary to lymphoma progression, 12 related to treatment toxicity, and 13 deemed unrelated to treatment or to lymphoma. 27 patients died during treatment (table 4). All but one of these patients had a performance status of 2 at baseline and nine had stage 4 disease (webappendix p 3). During follow-up, 25 patients died of lymphoma progression (webappendix p 2). Among the six patients who died without known disease progression in the follow-up period, three deaths were attributed to concurrent illness (one acute renal failure, one alteration of clinical status, and one stroke) and in three cases the cause of death was unknown. 77 patients had progression-free survival at the end of follow-up. Median progression-free survival was 21 months (95% CI 13 to upper limit not reached) and the 2-year progression-free survival rate was 47% (95% CI 38–56; figure 4).

Table 5 reports the responses at the end of treatment. Overall response rate was 73% and complete response or unconfirmed complete response rate was 62%. After

	2-year overall survival	Hazard ratio (95% CI)	Log-rank p value
Performance status ≥2	40·4% *vs* 68·4%	2·9 (1·8–4·9)	<0·0001
Ann Arbor stage III–IV	55·9% *vs* 68·5%	1·6 (0·8–2·9)	0·17
LDH concentration >618 U/L	54·4% *vs* 67·6%	1·6 (0·9–2·9)	0·12
Age-adjusted IPI 2–3	50·4% *vs* 74·7%	2·6 (1·4–4·9)	0·0024
Number of extranodal sites >1	45·1% *vs* 67%	2·1 (1·3–3·6)	0·0033
Serum albumin ≤35g/L	40·5% *vs* 80·4%	3·6 (1·9–6·6)	<0·0001
β2-microglobulin ≥3mg/L	59·6% *vs* 58%	1·1 (0·6–2·2)	0·69
Tumour mass >10 cm	30·3% *vs* 65·1%	2·2 (1·2–3·8)	0·0071
IADL score <4	52·7% *vs* 65·6%	1·8 (1·0–3·1)	0·0394

LDH=lactate dehydrogenase. IPI=international prognostic index. IADL= instrumental activities of daily living.

Table 2: **Univariate analyses of prognostic factors for overall survival**

	Hazard ratio (95% CI)	p value
Age-adjusted IPI 2–3	1·4 (0·6–3·5)	0·46
Number of extranodal sites >1	1·2 (0·6–2·4)	0·59
Serum albumin ≤35g/L	3·2 (1·4–7·1)	0·0053
β2-microglobulin ≥3mg/L	0·9 (0·4–1·9)	0·75
Tumour mass >10 cm	1·4 (0·6–2·9)	0·43
IADL score <4	1·9 (1·0–3·9)	0·064

IPI=international prognostic index. IADL=instrumental activities of daily living.

Table 3: **Multivariate analyses of prognostic factors for overall survival**

	Patients (n=149)	Causes
Cycle 1		
Deaths	13	..
Probably associated	4	3 sepsis with low neutrophils count; 1 acute renal failure
Possibly associated	1	Acute cardiac failure
Remotely associated	0	..
Unrelated	8	1 digestive bleeding, 1 chest pain with sudden death and 6 lymphoma progression
Unknown	0	..
Cycle 2		
Deaths	6	..
Probably associated	1	Oesophagobronchial fistulae
Possibly associated	2	1 clostridium difficile sigmoiditis and 1 unknown cause
Remotely associated	0	..
Unrelated	1	Sudden death
Unknown	2	..
Cycle 3		
Deaths	3	..
Probably associated	0	..
Possibly associated	1	Deterioration of general status
Remotely associated	0	..
Unrelated	2	1 infectious pneumopathy and one lymphoma progression
Unknown	0	..
Cycle 4		
Deaths	4	..
Probably associated	0	..
Possibly associated	2	1 deterioration of general status and 1 fungal pneumopathy
Remotely associated	0	..
Unrelated	2	1 femoral fracture and 1 lymphoma progression
Unknown	0	..
Cycle 5		
Deaths	0	..
Probably associated	0	..
Possibly associated	0	..
Remotely associated	0	..
Unrelated	0	..
Unknown	0	..
Cycle 6		
Deaths	1	..
Probably associated	1	Deterioration of general status
Possibly associated	0	..
Remotely associated	0	..
Unrelated	0	..
Unknown	0	..

Table 4: **Association of deaths with treatment during the treatment phase**

the third cycle, the overall response rate was the same but the complete response (n=31) or unconfirmed complete response (n=42) was 49%.

Of the 98 patients who attained a complete response or unconfirmed complete response at any time during treatment, 32 relapsed or died, resulting in a disease-free survival estimate of 57% at 2 years (95% CI 42–68%; median not reached; figure 5). 33 of the 43 patients who progressed or relapsed received salvage therapy; 24 had chemotherapy or immunotherapy and nine had radiotherapy. The overall response rate of salvage treatment was 27% (9/33), with 21% (7/33) of patients achieving a complete response or unconfirmed complete response. There was no recommended salvage therapy. Most common salvage chemotherapy regimens for patients who had progression or relapse were a combination of ifosfamide and etoposide (n=9), or gemcitabine and oxaliplatin (n=7).

The most common side-effect was haematological toxicity. Neutropenia was reported in 95 (64%) of 149 patients, 59 (40%) of whom had grade 3 toxicity or higher; thrombocytopenia was reported in 56 (38%) patients, 11 (7%) of whom had grade 3 toxicity or higher; and anaemia was reported in 133 (89%) of patients, 13 (9%) of whom had grade 3 toxicity or higher. G-CSF was given from the first cycle to 76 of 149 patients for a median of 5 days (range 1–8) per cycle. 11 patients had one or several episodes of febrile neutropenia (table 6). 36 (24%) of 149 patients had red blood cell transfusions and five (3%) had platelet transfusions. Patients spent a median of 2 days (range 0–46) in hospital during the first cycle and 0 (0–17) days during the next five cycles. 78 patients had a total of 155 adverse events, 148 of which occurred during the treatment period; 115 adverse events were grade 3 or higher and 70 were serious adverse events (table 7). The most common serious adverse events were infections (56 infections were grade 2 or higher), general disorders, and respiratory and mediastinal disorders. Five adverse reactions to rituximab infusion were recorded. Five (71%) of seven grade 3 to 4 thrombocytopenias, three (43%) of seven grade 3 to 4 febrile neutropenias, and seven (58%) of 12 grade 3 to 4 infections with low neutrophil counts occurred during the first cycle.

Discussion

In this phase 2 study of patients over 80 years old who have diffuse large B-cell lymphoma treated with an attenuated immunochemotherapy, we recorded a 29-month median overall survival and a 62% complete response and unconfirmed complete response rate. After the third cycle, the overall response rate was the same as at the end of treatment but the complete or unconfirmed complete response rate was lower than at the end of treatment, suggesting that some patients in partial remission achieved complete remission during the last three cycles. More than half of the patients who achieved a complete response were still in remission at 2 years. This treatment combination had an acceptable toxicity profile.

With the synergistic effects of the increase in lymphoma incidence and the ageing population, a large increase in the number of new lymphoma cases can be anticipated in elderly patients in the near future. The incidence of non-Hodgkin lymphoma in patients over 80 years is

 Published online April 8, 2011 DOI:10.1016/S1470-2045(11)70069-9

already higher than 100 per 100 000 in the USA.[24] Most of these cases are diffuse large B-cell lymphomas; thus, a treatment that provides optimum balance between efficacy and safety for these patients is needed.

Few data are available to compare with the findings from this study (panel). Before rituximab was available as a treatment option, complete remission rates in patients with diffuse large B-cell lymphomas ranged from 36% to 59% in retrospective studies but median survival was always shorter than 18 months.[3–5,9] These results compare unfavourably with those from patients aged 60–80 years who were treated with full-dose CHOP and rituximab, in whom the complete remission rate was 76% and median survival was more than 8 years.[14] Only 16 patients older than 80 years were included in the prospective ECOG trial of CHOP and rituximab.[16] However, in this study age greater than 70 years was a significant adverse factor.[25] Whether improved patient outcome results can be obtained in a selected group of patients aged over 80 years with full-dose R-CHOP remains to be shown. A different approach comprising abbreviated immunochemotherapy without doxorubicin followed by rituximab maintenance to treat elderly patients who are poor candidates for standard R-CHOP has been described recently.[26] In this study, the 2-year survival rate was 76% and the 22 patients who were over 80 years old had a shorter progression-free survival than the younger patients but a similar overall survival.

Several factors increase the risk of chemotherapy toxicity in the elderly. These include functional impairment, comorbidity, chronic undernutrition, cognitive decline, depression, and social isolation.[27] Elderly patients who were treated with standard CHOP, even associated with growth factor support, had a higher incidence of febrile neutropenic episodes than younger patients, despite being frequently given lower doses of chemotherapy or receiving fewer cycles of chemotherapy.[28–30] Unlike American Society of Clinical Oncology guidelines for elderly patients receiving standard R-CHOP, prophylactic use of G-CSF was not recommended systematically in the protocol because the rate of febrile neutropenia in our preliminary study[6] was only 6% and not the 20% recommended for the treatment. Despite the non-systematic use of G-CSF, 72% of the patients completed the planned treatment. Over 20% of the deaths reported during treatment and follow-up were related to treatment toxicity. The rates of death from toxicity reported in retrospective studies in this population ranged from 9% to 23%.[3–5] In our study, most grade 3–4 haematological toxicities, grade 3–4 infectious complications, and five treatment-related deaths occurred during the first cycle of treatment. To improve the performance status and tolerance of this cycle, in our future trial we will include a prephase treatment before the administration of the first full dose of treatment, as recommended by the German High-Grade Non-Hodgkin's Lymphoma Study Group.[31]

The only parameter associated with poor outcome in the multivariate analyses was a low serum albumin concentration. We and others have consistently found that this parameter is associated with patients at risk of poor outcome.[32–35] Low serum albumin concentration is associated with malnutrition, cytokine secretion, and advanced disease stage. Low serum albumin might be a good indicator of the ability of elderly patients with a good performance status to tolerate the treatment.[35]

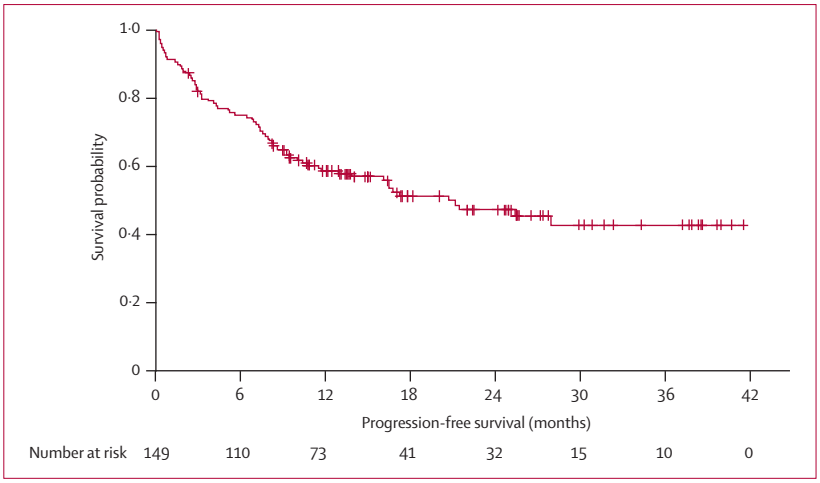

Figure 4: **Progression-free survival**

	Patients (n=149)
Complete response	59 (40%)
Unconfirmed complete response	34 (23%)
Partial response	16 (11%)
Stable disease	2 (1%)
Progression during treatment	8 (5%)
Death	27 (18%)
Not assessed	3 (2%)

Table 5: **Response at end of treatment**

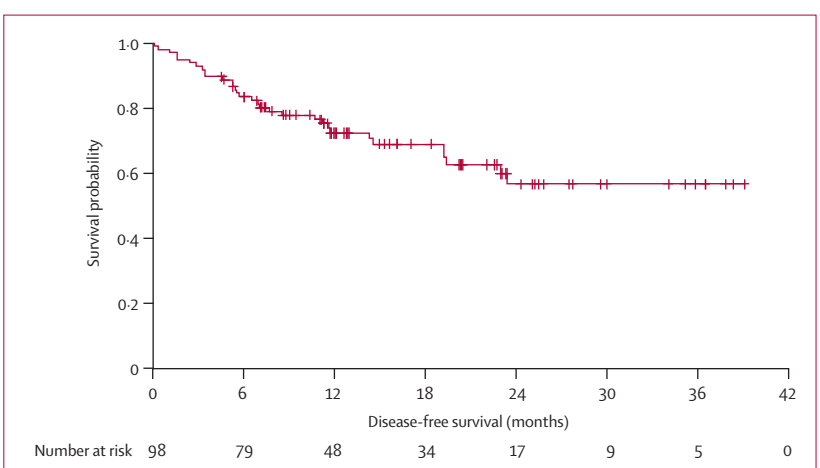

Figure 5: **Disease-free survival**
Only patients who attained a complete response or an unconfirmed complete response during treatment are included.

	No toxicity	Grade 1–2	Grade 3	Grade 4	Grade 5
Infection without neutropenia	113 (76%)	22 (15%)	12 (8%)	0 (0%)	2 (1%)
Febrile neutropenia	138 (93%)	1 (1%)	7 (5%)	0 (0%)	3 (2%)
Constitutional symptoms	69 (46%)	68 (46%)	7 (5%)	2 (1%)	3 (2%)
Neurological toxicity	109 (73%)	30 (20%)	7 (5%)	3 (2%)	0 (0%)
Pulmonary toxicity	118 (79%)	25 (17%)	4 (3%)	1 (0%)	1 (1%)
Renal toxicity	137 (92%)	8 (5%)	2 (1%)	1 (0%)	1 (1%)
Cardiac arrhythmia	134 (90%)	11 (7%)	2 (1%)	2 (1%)	0 (0%)
Cardiac (other)	133 (89%)	13 (9%)	2 (1%)	0 (0%)	1 (1%)
Vascular toxicity	137 (92%)	8 (5%)	3 (2%)	1 (1%)	0 (0%)
Mucositis	138 (93%)	11 (7%)	0 (0%)	0 (0%)	0 (0%)
Creatinine	117 (79%)	31 (21%)	0 (0%)	1 (1%)	0 (0%)
Transaminases	128 (86%)	20 (13%)	0 (0%)	1 (1%)	0 (0%)

Data are number (%). Percentages do not add up to 100% in some cases because of rounding.

Table 6: **Incidence of non-haematological toxicity by grade**

	Serious adverse event (n=70)
Infections and infestations	19 (27%)
General disorders	12 (17%)
Respiratory and mediastinal disorders	10 (14%)
Gastrointestinal disorders	7 (10%)
Nervous system disorders	7 (10%)
Renal and urinary disorders	4 (6%)
Cardiac and vascular disorders	4 (6%)
Injury and procedural complications	3 (4%)
Hepatobiliary disorders	2 (3%)
Skin disorders	1 (1%)
Musculoskeletal tissue disorders	1 (1%)

Data are number (%). Percentages do not add up to 100% because of rounding.

Table 7: **Serious adverse events**

Panel: Research in context

Systematic review

We searched PubMed with no date limitations set for articles with the search terms "lymphoma, large B-cell, diffuse", "elderly", and "geriatric evaluation".

Although many clinical trials have described outcome in patients over 60 years old who have diffuse large B-cell lymphoma, we were unable to identify prospective studies in patients older than 80 years. We identified four retrospective studies in this specific population.[3-6] These studies suggested that a significant proportion of patients could benefit from an adapted regimen of chemotherapy.

Interpretation

Our results provide evidence that an association of low-dose chemotherapy with standard rituximab might give a substantial response and survival benefit in selected patients aged over 80 years and that some very elderly patients could experience prolonged survival. R-miniCHOP should be the standard treatment for patients older than 80 years who have diffuse large B-cell lymphoma and a good performance status.

We used IADL to assess patient ability to tolerate immunochemotherapy but we did not do a comprehensive geriatric assessment because the use of such an assessment has not been shown to affect overall survival. In univariate analyses, an impaired IADL score was associated with poor survival, as was recently described in an observational study,[36] and is independent from ECOG.[37] IADL is easier to do in daily routine than the comprehensive geriatric assessment, but whether it could be used to select patients for curative treatment remains to be shown.[27,38]

Despite the absence of a control arm, this study suggests that in selected patients older than 80 years who have diffuse large B-cell lymphoma and a good performance status, immunochemotherapy with R-miniCHOP offers a good compromise between efficacy and safety, which suggests that a substantial proportion of elderly patients can be cured. This regimen could be considered as a platform for the introduction of new targeted drugs in the first-line treatment of this population.[39]

Contributors

FP, AT, CH, and HT, designed the study. FP, FJ, CT, AT, SC, BC, CH, SB, OF, GL, CF, DB, MB, RD, MJ, BS, MA, MF, and HT collected the data. FP, AT, J-FE, BC, MF, PG, and HT analysed and interpreted the data. FP, FJ, AT, BC, and HT wrote the report. All authors had full access to the final version of the report and agreed to the submission.

Conflicts of interest

The Groupe d'Etude des Lymphomes de l'Adulte (GELA) was supported by Amgen to conduct this study with an unrestricted grant. BC has received payment for lectures from Roche and is a Roche board member. CH is a board member for Celgene, Pfizer, Roche, and Janssen and has received payment for educational presentations from Roche. RD has received consultancy fees from Roche and is a board member for Roche and Celgene. HT is a board member for Celgene, Genentech, and Seattle Genetics; has received grants from Celgene and Amgen; has received payment for lectures from Pfizer, Janssen, Celgene, and Amgen. All other authors declared no conflicts of interest.

Acknowledgments

This study was funded by the GELA, France. The findings of the study have been presented previously at the 52nd Annual Meeting of the American Society of Hematology, Orlando, FL, USA. Dec 4–7, 2010. We thank the investigators who participated in this trial; members of the reference pathology panel: Pascal Cuillère-Dartigues, Bettina Fabiani, Jean-François Emile, and Philippe Gaulard; and members of GELA-RC: Camille Pitrou, Laurence Girard, Carole Mancien, Flore Allemandou, Karina Dordonne, Pascale Godard, Marie-Laure Prunet, Larissa Mege, Nadine Vailhen, and Christine Lovera from Centre Antoine Lacassagne, Nice, France, for their support during the study.

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