CHOP CHEMOTHERAPY PLUS RITUXIMAB COMPARED WITH CHOP ALONE IN ELDERLY PATIENTS WITH DIFFUSE LARGE-B-CELL LYMPHOMA

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ABSTRACT

Background The standard treatment for patients with diffuse large-B-cell lymphoma is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Rituximab, a chimeric monoclonal antibody against the CD20 B-cell antigen, has therapeutic activity in diffuse large-B-cell lymphoma. We conducted a randomized trial to compare CHOP chemotherapy plus rituximab with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.

Methods Previously untreated patients with diffuse large-B-cell lymphoma, 60 to 80 years old, were randomly assigned to receive either eight cycles of CHOP every three weeks (197 patients) or eight cycles of CHOP plus rituximab given on day 1 of each cycle (202 patients).

Results The rate of complete response was significantly higher in the group that received CHOP plus rituximab than in the group that received CHOP alone (76 percent vs. 63 percent, $P=0.005$). With a median follow-up of two years, event-free and overall survival times were significantly higher in the CHOP-plus-rituximab group ($P<0.001$ and $P=0.007$, respectively). The addition of rituximab to standard CHOP chemotherapy significantly reduced the risk of treatment failure and death (risk ratios, 0.58 [95 percent confidence interval, 0.44 to 0.77] and 0.64 [0.45 to 0.89], respectively). Clinically relevant toxicity was not significantly greater with CHOP plus rituximab.

Conclusions The addition of rituximab to the CHOP regimen increases the complete-response rate and prolongs event-free and overall survival in elderly patients with diffuse large-B-cell lymphoma, without a clinically significant increase in toxicity. (N Engl J Med 2002;346:235-42.)

THE most frequent type of non-Hodgkin's lymphoma, diffuse large-B-cell lymphoma, accounts for approximately 40 percent of new cases of lymphoma.[1] More than half of patients with diffuse large-B-cell lymphoma are over 60 years of age,[2-4] and the treatment of these elderly patients is a difficult challenge. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) is the standard of care for younger and elderly patients with diffuse large-B-cell lymphoma,[5] but it induces complete responses in only 40 to 50 percent of elderly patients, with three-year event-free and overall survival rates of 30 percent and 35 to 40 percent, respectively.[6] Attempts to increase the efficacy of CHOP by adding other cytotoxic drugs have not succeeded, probably because these additional drugs cannot be administered unless the doses of cyclophosphamide and doxorubicin are reduced below those given in the CHOP regimen.[5,7] Intensified chemotherapy regimens may improve the outcome in young patients with a poor prognosis,[8] but they are not well tolerated by elderly patients. Indeed, CHOP itself may be too toxic for elderly patients.[9,10] More easily tolerated regimens have been designed for elderly patients, but although they cause fewer side effects, they are less effective and no more beneficial than CHOP.[6,11]

Rituximab, a chimeric anti-CD20 IgG1 monoclonal antibody, is effective when given as a single agent in the treatment of relapsed or refractory indolent lymphomas and has activity in relapsed or refractory diffuse large-B-cell lymphoma.[12-15] CD20 is a cell-surface protein that occurs almost exclusively on mature B cells. The chimeric antibody is a human IgG1 in which the CD20-binding region was derived by genetic engineering from a mouse monoclonal antibody. On the basis of phase 2 studies in which rituximab in combination with CHOP had a good safety profile and induced responses in over 90 percent of patients with indolent or aggressive lymphoma,[16,17] the Groupe d'Etude des Lymphomes de l'Adulte (GELA) undertook a study to compare CHOP plus rituximab with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.

METHODS

Patients

Patients were eligible if they were 60 to 80 years of age and had untreated diffuse large-B-cell lymphoma that had been diagnosed according to the Revised European–American Lymphoma clas-

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sification[18] or the World Health Organization classification.[19] Patients were required to have stage II, III, or IV disease and a performance status of 0 to 2 (good to fair) according to the criteria of the Eastern Clinical Oncology Group. Patients were not eligible if they had T-cell lymphoma, a history of indolent lymphoma, central nervous system involvement, active cancer, or any serious active concomitant disease or if, in the opinion of the investigator, their general status did not permit the administration of eight courses of CHOP. Patients were also excluded if they had a cardiac contraindication to doxorubicin therapy (e.g., abnormal contractility on echocardiography) or a neurologic contraindication to vincristine (e.g., peripheral neuropathy). Finally, patients with a positive serologic test for the human immunodeficiency virus or unresolved hepatitis B virus infection were also excluded.

This study complied with all provisions of the Declaration of Helsinki and its current amendments and was conducted in accordance with Good Clinical Practice guidelines.[20] All patients gave written informed consent. The protocol and informed-consent forms were approved by the local and national institutional review boards in each participating center and country. Study oversight was provided by an independent data and safety monitoring committee. The study investigators are listed in the Appendix.

Randomization

Eligible patients were randomly assigned by the study coordinating center to treatment with CHOP or CHOP plus rituximab. They were stratified according to center and age-adjusted International Prognostic Index scores (0 or 1 vs. 2 or 3, with a higher score indicating a higher risk of death), which are based on disease stage, performance status, and the lactate dehydrogenase level.[2] A panel of at least three hematopathologists conducted a central pathology review, without knowledge of the patients' outcome, to confirm the diagnosis of CD20-positive diffuse large-B-cell lymphoma.

Treatment

Patients treated with CHOP received the combination of 750 mg of cyclophosphamide per square meter of body-surface area on day 1; 50 mg of doxorubicin per square meter on day 1; 1.4 mg of vincristine per square meter, up to a maximal dose of 2 mg, on day 1; and 40 mg of prednisone per square meter per day for five days. They were treated every three weeks for eight cycles of CHOP. Patients treated with CHOP plus rituximab also received rituximab, at a dose of 375 mg per square meter, on day 1 of each of the eight cycles of CHOP. The rituximab infusion was interrupted in the event of fever, chills, edema, congestion of the head and neck mucosa, hypotension, or any other serious adverse event and was resumed when such an event was no longer occurring. No radiation therapy was scheduled or recommended at the end of treatment.

Patients who had grade 4 (severe) neutropenia or febrile neutropenia after any cycle of chemotherapy were given granulocyte colony-stimulating factor. If grade 4 neutropenia persisted during the next cycle, the doses of cyclophosphamide and doxorubicin were decreased by 50 percent. For patients with grade 3 (moderate) or 4 thrombocytopenia, the doses of cyclophosphamide and doxorubicin were decreased by 50 percent. If the neutrophil count was lower than 1500 per cubic millimeter or the platelet count was lower than 100,000 per cubic millimeter before a scheduled cycle, the cycle was delayed for up to two weeks, and then treatment was stopped. The doses of rituximab were not modified, but rituximab was discontinued when CHOP was stopped. Treatment was stopped if lymphoma progressed or the patient declined to continue or at the discretion of the investigator in cases of intercurrent illness or adverse events.

Response to Treatment and Adverse Events

Tumor responses were assessed after eight cycles of chemotherapy or at the end of treatment and were classified as complete response, unconfirmed complete response, partial response, stable disease, or progressive disease according to the International Workshop criteria.[21] Complete response was defined as the disappearance of all lesions and of radiologic or biologic abnormalities observed at diagnosis and the absence of new lesions. An unconfirmed complete response was defined as a complete response with the persistence of some radiologic abnormalities, which had to have regressed in size by at least 75 percent. Partial response was defined as the regression of all measurable lesions by more than 50 percent, the disappearance of nonmeasurable lesions, and the absence of new lesions. Stable disease was defined as a regression of any measurable lesion by 50 percent or less or no change for the nonmeasurable lesions, but without growth of existing lesions or the appearance of new lesions. Progressive disease was defined as the appearance of a new lesion, any growth of the initial lesion by more than 25 percent, or growth of any measurable lesion that had regressed during treatment by more than 50 percent from its smallest dimensions.

All adverse events reported by the patient or observed 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 base-line condition, whether it was considered related to treatment or not. Each event was graded according to the National Cancer Institute Common Toxicity Criteria grading system.[22] All grade 3 and 4 events plus grade 2 infection were recorded in detail. Grade 1 and 2 adverse events were not extensively described.

Statistical Analysis

The sample size was calculated on the basis of the primary end point of event-free survival, and the number of patients required was based on the assumption of an exponential distribution of events. On the basis of the results of previous studies with CHOP in elderly patients, a conservative three-year event-free survival of 30 percent was assumed for the CHOP regimen.[23,24] To detect a change from 30 percent to 45 percent with the addition of rituximab, we calculated that 400 patients, recruited over three years and followed for a minimum of one year, would be required to provide the study with 80 percent power at an overall 5 percent significance level (two-sided, with an alpha level of 0.05). A single interim analysis of the primary efficacy outcome was planned; it included the 328 patients who underwent randomization before January 1, 2000.[25]

Event-free and overall survival was analyzed by the log-rank test, and the results were expressed as Kaplan–Meier plots. A multivariate Cox regression analysis was performed to assess the effect of pretreatment prognostic factors (specifically, age, sex, number of extranodal sites, presence or absence of bone marrow involvement, $beta_2$-microglobulin level, serum albumin level, presence or absence of bulky disease, B symptoms [weight loss, fever, and night sweats]), and age-adjusted International Prognostic Index scores) on event-free and overall survival. Estimates of the treatment effect, after adjustment for these prognostic factors, are expressed as risk ratios for event-free and overall survival (CHOP plus rituximab as compared with CHOP), with 95 percent confidence intervals. Analyses of efficacy and safety included all randomized patients and followed the intention-to-treat principle. All P values are two-tailed. Statistical analyses were performed with SAS software (SAS Institute, Cary, N.C.) by the investigators at the GELA statistical office, without restrictions or outside control by the sponsor. The investigators had complete access to all study data.

RESULTS

This study was conducted at 86 centers in France, Belgium, and Switzerland. A total of 399 patients were enrolled between July 1998 and March 2000, and 398 patients (202 in the CHOP-plus-rituximab

group and 196 in the CHOP group) received at least one dose of protocol-specified treatment (1 patient was enrolled but died before treatment was administered).

Base-Line Characteristics

The median age of the patients was 69 years. There was no significant difference between the two groups in any clinical or pathological characteristic (Table 1). Prognosis was poor, which is consistent with the prognosis in elderly patients with aggressive lymphoma. Central pathological review was completed for 97 percent of patients; the results confirmed a diagnosis of diffuse large-B-cell lymphoma in 90 percent of those who could be assessed in the CHOP-plus-rituximab group and 85 percent in the CHOP group.

Treatment

The eight scheduled courses of chemotherapy were given to 72 percent of patients treated with CHOP and 80 percent of patients treated with CHOP plus rituximab. This difference was due to the number of patients who withdrew from the CHOP group because of disease progression: 23, as compared with 7 of those treated with CHOP plus rituximab. In each treatment cycle, more than 90 percent of the patients received at least 90 percent of the planned doses of doxorubicin and cyclophosphamide, with no significant difference between treatment groups in dose intensity for either drug in any cycle. In the CHOP-plus-rituximab group, more than 95 percent of the patients received the planned dose of rituximab.

Efficacy

With a median follow-up of 24 months, 86 events (progression, relapse, or death) were observed in the CHOP-plus-rituximab group and 120 in the CHOP group (in 43 percent and 61 percent of patients, respectively) (Table 2 and Fig. 1). Event-free survival was significantly longer for patients treated with CHOP plus rituximab than for those treated with CHOP alone ($P<0.001$). According to the Cox analysis, the regimen of CHOP plus rituximab reduced the risk of events by 42 percent, as compared with the risk with CHOP alone (Table 2). The difference in event-free survival between the treatment groups was attributable to the higher number of patients in the CHOP group who had disease progression during treatment or with relapse. There was a significant benefit of CHOP plus rituximab over CHOP alone, both among patients with relatively low risk disease, indicated by a score of 0 or 1 on the International Prognostic Index ($P<0.001$), and those with high-risk disease, indicated by a score of 2 or 3 on the International Prognostic Index ($P<0.03$). Patients younger

TABLE 1. CHARACTERISTICS OF THE 399 PATIENTS.*

CHARACTERISTIC	CHOP PLUS RITUXIMAB (N=202)	CHOP (N=197)
	no. (%)	
Age		
<65 yr	44 (22)	48 (24)
65–69 yr	57 (28)	62 (31)
70–74 yr	52 (26)	56 (28)
≥75 yr	49 (24)	31 (16)
Male sex	92 (46)	107 (54)
Performance status†		
0	67 (33)	70 (36)
1	90 (45)	94 (48)
>1	45 (22)	33 (17)
Stage		
I	0	1 (1)
II	41 (20)	39 (20)
III	33 (16)	29 (15)
IV	128 (63)	128 (65)
B symptoms‡	78 (39)	70 (36)
No. of extranodal sites		
0	46 (23)	44 (22)
1	95 (47)	102 (52)
>2	61 (30)	51 (26)
Bulky tumor (>10 cm)	60 (30)	64 (32)
Bone marrow involvement	56 (28)	55 (28)
Elevated lactate dehydrogenase	131 (65)	132 (67)
Histologic findings		
Not reviewed	6 (3)	8 (4)
Reviewed	196 (97)	189 (96)
Diffuse large-B-cell lymphoma	176 (87)	160 (81)
Not diffuse large-B-cell lymphoma	20 (10)	29 (15)
Burkitt's lymphoma	2	2
Mantle-cell lymphoma	4	4
Marginal-zone lymphoma	2	1
Follicular lymphoma	5	10
Small lymphocytic lymphoma	1	6
B-cell lymphoma, unspecified		2
T-cell lymphoma	4	3
Hodgkin's lymphoma	2	1
Age-adjusted International Prognostic Index score§	20 (10)	21 (11)
0	61 (30)	56 (28)
1	87 (43)	94 (48)
2	34 (17)	26 (13)
3		
Standard International Prognostic Index score§	29 (14)	23 (12)
0–1	64 (32)	69 (35)
2	78 (39)	82 (42)
3	31 (15)	23 (12)
4–5		

*CHOP denotes cyclophosphamide, doxorubicin, vincristine, and prednisone. None of the differences between treatment groups were significant (i.e., $P<0.05$).

†Performance status was defined according to the criteria of the Eastern Clinical Oncology Group (with an increasing score indicating declining performance).

‡B symptoms were defined as weight loss, fever, and night sweats.

§Higher scores indicate a higher risk of death.

TABLE 2. RESULTS OF THE INTENTION-TO-TREAT ANALYSIS OF END POINTS.*

END POINT	CHOP PLUS RITUXIMAB (N=202)	CHOP (N=197)	P VALUE
Event — no. (%)†	86 (43)	120 (61)	0.002
Progression during treatment	19 (9)	44 (22)	
New alternative treatment	11 (5)	9 (5)	
Progression after stable disease	1 (<1)	1 (1)	
Progression after partial response	5 (2)	4 (2)	
	29 (14)	49 (25)	
Relapse	21 (10)	13 (7)	
Death without progression	12 (6)	11 (6)	
During treatment	9 (4)	2 (1)	
After treatment			
Median time to event — mo	NR	13	<0.001
Relative risk of event‡	0.58 (0.44–0.77)		
2-Yr event-free survival — %‡	57 (50–64)	38 (32–45)	
Median survival — mo	NR	NR	0.007
Relative risk of death‡	0.64 (0.45–0.89)		
Death — no. (%)	59 (29)	81 (41)	
2-Yr survival — %‡	70 (63–77)	57 (50–64)	

*The primary efficacy end point was event-free survival. Events were defined as disease progression or relapse, institution of a new anticancer treatment, or death from any cause without progression. Secondary efficacy end points were overall survival, response rates, and toxic effects. Event-free and overall survival was calculated as the time from randomization to the date of first reported event or death, respectively. Data from patients with no reported event were censored as of the most recent assessment or at the cutoff date for the analysis (June 30, 2001). CHOP denotes cyclophosphamide, doxorubicin, vincristine, and prednisone, and NR not reached.

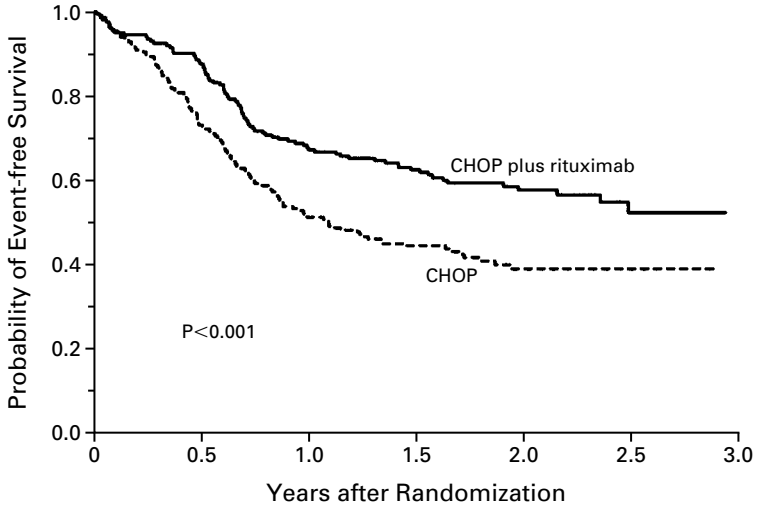
†Because of rounding, not all percentages total 100.

‡Values in parentheses are 95 percent confidence intervals.

than 70 years and those 70 years or older, as well as the patients with diffuse large-B-cell lymphoma, had the same benefit from the combination of CHOP plus rituximab (data not shown).

A complete response or unconfirmed complete response was achieved in 76 percent of the patients treated with CHOP plus rituximab, as compared with 63 percent of those treated with CHOP alone (P=0.005) (Table 3). Disease progression during treatment was reported for 22 percent of patients in the CHOP group and 9 percent in the CHOP-plus-rituximab group. Prolongation of disease-free survival (complete remission) and progression-free survival in the CHOP-plus-rituximab group was of the same magnitude as the prolongation of event-free survival (data not shown). Survival was significantly longer for patients treated with CHOP plus rituximab than for those treated with CHOP alone (P=0.007): at two years, 70 percent of patients treated with CHOP plus rituximab were alive, as compared with 57 percent of those treated with CHOP alone (Table 2 and Fig. 2).

Base-line prognostic factors were analyzed by multivariate Cox regression analysis. A high concentration (more than 3 mg per liter) of beta$_2$-microglobulin was identified as a negative prognostic factor in terms of both event-free and overall survival (risk ratio, 1.58 [95 percent confidence interval, 1.14 to 2.21] for death, disease progression, or another



NO. AT RISK						
CHOP plus rituximab	202	177	137	108	63	19
CHOP	197	144	101	72	42	17

Figure 1. Event-free Survival among 399 Patients Assigned to Chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) or with CHOP plus Rituximab.

TABLE 3. RESPONSE TO TREATMENT WITH CHOP OR CHOP PLUS RITUXIMAB.*

RESPONSE	CHOP PLUS RITUXIMAB (N=202)	CHOP (N=197)
	no. (%)	
Complete response	106 (52)	72 (37)
Unconfirmed complete response	46 (23)	52 (26)
Partial response	15 (7)	11 (6)
Stable disease	2 (1)	1 (1)
Progressive disease	19 (9)	43 (22)
Death without progression	12 (6)	11 (6)
Could not be assessed†	2 (1)	7 (4)

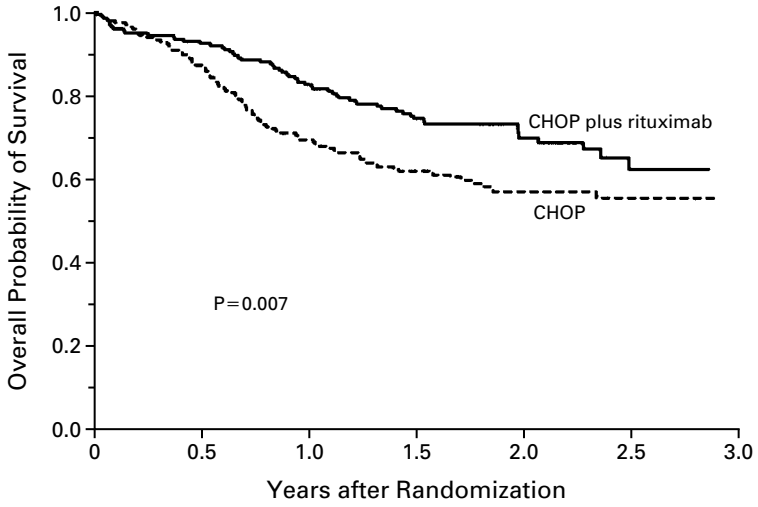
*Tumor responses were classified as complete response, unconfirmed complete response, partial response, stable disease, or progressive disease according to the International Workshop criteria.[21] CHOP denotes cyclophosphamide, doxorubicin, vincristine, and prednisone.

†Treatment was stopped because of toxic effects, the patient's decision, or the investigator's decision before evaluation of the tumor.

event and 1.82 [1.22 to 2.72] for death from any cause, respectively). The presence of more than one extranodal site of disease was another significant negative prognostic factor in terms of overall survival (risk ratio for death from any cause, 1.46). After adjustment for these prognostic factors, the risk ratio associated with treatment with CHOP plus rituximab, as compared with CHOP alone, was 0.55 (95 percent confidence interval, 0.41 to 0.75) for death, disease progression, or another event and 0.53 (0.37 to 0.77) for death from any cause, as compared with the unadjusted values of 0.58 (0.44 to 0.77) and 0.64 (0.45 to 0.89), respectively.

Adverse Effects

Table 4 presents all reported adverse events in each group. The grade 3 and 4 adverse events were consistent with the expected toxic effects of CHOP chemotherapy and occurred with similar frequency in both groups. Infection was one of the most frequent grade 3 or 4 adverse events in both groups. The difference in the incidence of cardiac events during treatment (47 percent for CHOP plus rituximab, as compared with 35 percent for CHOP) (Table 4) was due to a higher incidence of grade 1 events in the CHOP-plus-rituximab group than in the CHOP group (24 percent vs. 13 percent). This difference was consistent with the mild-to-moderate infusion-related events described in phase 2 studies of rituximab.[12-14,26] The incidence of grade 3 or 4 cardiac toxicity was the same in both groups (8 percent), with more reports of supraventricular arrhythmias and tachycardias in the CHOP-plus-rituximab group. Grade 3 or 4 cardiac failure or left ventricular dysfunction occurred in 18 patients in the CHOP-plus-rituximab group and 19 patients in the CHOP group.



NO. AT RISK						
CHOP plus rituximab	202	187	167	118	64	21
CHOP	197	171	136	96	58	16

Figure 2. Overall Survival among 399 Patients Assigned to Chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) or with CHOP plus Rituximab.

TABLE 4. NONHEMATOLOGIC ADVERSE EVENTS OBSERVED IN PATIENTS TREATED WITH CHOP PLUS RITUXIMAB OR CHOP ALONE.*

EVENT	ANY GRADE		GRADE 3 OR 4	
	CHOP PLUS RITUXIMAB	CHOP	CHOP PLUS RITUXIMAB	CHOP
	percentage of patients with an event in at least 1 cycle			
Fever	64	59	2	5
Infection	65	65	12	20
Mucositis	27	31	3	2
Liver toxicity	46	46	3	5
Cardiac toxicity	47	35	8	8
Neurologic toxicity	51	54	5	9
Renal toxicity	11	14	1	2
Lung toxicity	33	30	8	11
Nausea or vomiting	42	48	4	8
Constipation	38	41	2	5
Alopecia	97	97	39	45
Other toxicities	84	80	20	25

*All adverse events reported by the patient or observed by the investigator were recorded. An adverse event was defined as any adverse change from the patient's base-line condition, whether it was considered related to treatment or not. Each event was graded according to the National Cancer Institute Common Toxicity Criteria grading system; higher numbers denote more severe toxicity. CHOP denotes cyclophosphamide, doxorubicin, vincristine, and prednisone.

Grade 3 or 4 adverse events related to the infusion of rituximab were observed in 19 patients in the CHOP-plus-rituximab group (9 percent); the most frequent of these were respiratory symptoms (with or without bronchospasm), chills, fever, and hypotension. In all cases, the symptoms disappeared after the infusion was slowed or stopped, and no patient died as a result of such an adverse event. All patients were able to receive further cycles of CHOP plus rituximab without recurrence of grade 3 or 4 infusion-related reactions.

Thirty-four patients (13 in the CHOP group and 21 in the CHOP-plus-rituximab group) died from causes not attributable to lymphoma; 23 died during the treatment period from infection (16 patients), cachexia (4 patients), or cardiovascular events (3 patients), without any significant difference between the groups. The remaining 11 patients (2 in the CHOP group and 9 in the CHOP-plus-rituximab group) died from infection (4 patients), cachexia (2 patients), cardiac disease (2 patients), suicide (1), another type of cancer (1), or gastrointestinal hemorrhage (1) while in a complete remission after completing therapy.

The median nadir of the neutrophil count after each cycle of chemotherapy was similar in both groups. After the first cycle, neutrophil counts fell to 400 per cubic millimeter in both groups. Thereafter, the median was slightly higher in the CHOP group than in the CHOP-plus-rituximab group. Neutropenia was not associated with an increase in episodes of infection during treatment, as shown in Table 4. The percentages of patients who required treatment with granulocyte colony-stimulating factor increased to a similar degree in each treatment group, to 37 percent for the fourth cycle and 43 percent for the eighth cycle. There were a few more cases of herpes zoster after treatment in patients receiving CHOP plus rituximab than in those receiving CHOP (nine vs. two, $P=0.40$). During treatment, 19 percent of patients receiving CHOP and 14 percent of those receiving CHOP plus rituximab had grade 3 or 4 anemia. The median nadir platelet counts remained above 130,000 per cubic millimeter in both treatment groups for all eight cycles.

DISCUSSION

This randomized trial compared the efficacy and safety of rituximab in combination with CHOP chemotherapy with that of CHOP chemotherapy alone in elderly patients with diffuse large-B-cell lymphoma. We found higher response rates and improved event-free and overall survival among patients treated with the combination of rituximab and CHOP. The longer survival in the CHOP-plus-rituximab group was due to a lower rate of disease progression during therapy and fewer relapses among patients who had a complete response. Treatment with CHOP plus rituximab was well tolerated, and the incidence of severe or serious adverse events was no different from that in the CHOP group.

The event-free survival among elderly patients with diffuse large-B-cell lymphoma was only 12 to 18 months in previous randomized studies of chemotherapy.[6,9,24] We chose CHOP for use in this study because it is as effective as, and less toxic than, other, more recently developed chemotherapeutic regimens[5,27,28]; it is also considered to be standard therapy for elderly patients with diffuse large-B-cell lymphoma.[6,11,29] The results with CHOP alone in our trial were similar to those previously reported in elderly patients.[6,9-11,23,29] For this reason, we believe that the better results with CHOP plus rituximab are not attributable to an unusually poor outcome among patients in the CHOP group.

In a study comparing a regimen of doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVB) with CHOP in elderly patients, we found that ACVB was associated with longer event-free survival because patients who received ACVB had a lower incidence of relapses.[23] However, the rate of death due to toxic effects of the therapy was higher with ACVB than with CHOP, particularly in pa-

tients over 65 years of age, and for this reason, treatment with ACVB was not associated with prolonged survival.

In conclusion, the addition of rituximab to CHOP chemotherapy, given for eight cycles to elderly patients with newly diagnosed diffuse large-B-cell lymphoma, significantly increases the rate of complete response, decreases the rates of treatment failure and relapse, and improves event-free and overall survival as compared with standard CHOP alone. These gains were achieved without a significant increase in clinically significant toxic effects.

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Drs. Coiffier, Salles, Reyes, and Gisselbrecht have served as consultants to Roche, Genentech, or IDEC, the manufacturers of rituximab; have been members of speakers' bureaus sponsored by Roche, Genentech, or IDEC; or have done both for Roche, Genentech, or IDEC, as well as for other companies involved in the manufacture of antilymphoma drugs or other monoclonal antibodies.

APPENDIX

The following persons and institutions participated in this GELA study: External advisory committee — E. Montserrat (chairman, Spain), M. Björkholm (Sweden), M. Buyse (Belgium), F. Cavalli (Switzerland), and M. Pfreundschuh (Germany); Pathological review committee — J. Brière, P. Gaulard, J. Bosq, J.F. Emile, B. Fabiani, and T. Petrella; Statistics — E. Lepage and N. Nio; Pharmacist — I. Madelaine; GELA clincial research — R. Chvetzoff; study centers (all in France, unless otherwise specified) — Centre Hospitalier Lyon-Sud, Pierre-Bénite — B. Coiffier and G. Salles; Hôpital de Hautepierre, Strasbourg — R. Herbrecht; Centre Becquerel, Rouen — H. Tilly; Centre Jean Bernard, Le Mans — P. Solal-Celigny; Institut Paoli Calmette, Marseilles — R. Bouabdallah; Centre Hospitalier Universitaire de Brabois, Nancy — P. Lederlin; Centre Léon Bérard, Lyons — C. Sebban; Institut Gustave Roussy, Villejuif — J.N. Munck and C. Fermé; Centre Hospitalier de Lens, Lens — P. Morel; Hôpital Henri Mondor, Creteil — F. Reyes and C. Haioun; Centre Hospitalier de Chambéry, Chambéry — M. Blanc; Hôpital Bon Secours, Metz — B. Christian; Centre Hospitalier Universitaire de Lille, Lille — B. Quesnel; Academisch Ziekenhuis Sint-Jan, Bruges, Belgium — A. van Hoof; Hôpital Saint-Louis, Paris — C. Gisselbrecht; Hôpital Purpan, Toulouse — M. Attal; Centre Hospitalier Universitaire Dupuytren, Limoges — D. Bordessoule; Hôpital Jean Bernard, Poitiers — V. Delwail; Université Catholique de Louvain, Ivoir, Belgium — A. Bosly; Centre Hospitalier Universitaire Clemenceau, Caen — M. Macro; Centre François Magendie, Pessac — G. Marit; Hôpital Pitié Salpétrière, Paris — J. Gabarre; Hôpital André Mignot, Le Chesnay — S. Castaigne; Centre Hospitalier Universitaire de Nîmes, Nîmes — E. Jourdan; Centre Hospitalier de la Durance, Avignon — E. Lepeu; Hôpital Pasteur, Colmar — B. Audhuy; Centre Antoine Lacassagne, Nice — A. Thyss; Clinique Pasteur, Evreux — N. Albin; Centre Médical Foch, Suresnes — E. Baumelou; Hôtel Dieu, Paris — A. Delmer; Centre Hospitalier de Brive, Brive — S. Lefort; Centre Hospitalier de Bourg en Bresse, Bourg en Bresse — H. Orfeuvre; Hôpital V. Prouvo, Roubaix — I. Plantier; Hôpital Bicêtre, Le Kremlin-Bicêtre — G. Tertian; Hôpital Necker, Paris — B. Varet; Hôpital Beclere, Clamart — F. Boué; Centre Hospitalier Universitaire de Dijon, Dijon — O. Casasnovas and D. Caillot; Université Catholique de Louvain, Brussels, Belgium — E. Van Den Neste; Institut Curie, Paris — D. Decaudin; Centre Hospitalier Universitaire Saint-Louis–Lariboisière, Paris — P. Brice, H. Dombret, J.P. Fermand, and J.M. Zini; Centre Hospitalier Universitaire de Liège, Liège, Belgium — G. Fillet; Fondation Drevon, Dijon — M. Flesch; Centre Hospitalier R. Dubos, Pontoise — Y. Kerneis; Centre Hospitalier d'Annecy, Annecy — C. Martin; Hôpital de Valence, Valence — P.Y. Péaud; Centre Hospitalier de Blois, Blois — P. Rodon; Centre Hospitalier Saint-Vincent, Lille — C. Rose; Hôtel Dieu, Clermont-Ferrand — P. Travade; Clinique Saint-Jean, Lyons — B. Velay; Hôpital de Bayonne, Bayonne — F. Bauduer; Centre Hospitalier de Libourne, Libourne — K. Bouabdallah; Hôpital Emile Muller, Mulhouse — J.C. Eisenmann; Hôpital Marc Jacquet, Melun — C. Kulekci; Centre Hospitalier Bois de l'Abbaye, Seraing, Belgium — S. Lampertz; Hôpital Inter Armées Percy, Clamart — G. Nedellec; Centre François Baclesse, Caen — A.M. Peny; Centre Hospitalier Victor Dupouy, Argenteuil — V. Pulik; Hôpital de Chalon, Chalon — B. Salles; Centre Hospitalier de Perpignan, Perpignan — X. Vallantin; Centre Hospitalier Robert Ballanger, Aulnay sous Bois — P. Agranat; Centre Hospitalier Universitaire de Nice, Nice — J.P. Cassuto; Centre Hospitalier Hutois, Huy, Belgium — J. Collignon; Centre Hospitalier de la Citadelle, Liège, Belgium — B. de Prijck; Hôpital Jolimont, Haine Saint Paul, Belgium — A. Delannoy; Centre Hospitalier Gilles de Corbeil, Corbeil Essonnes — A. Devidas; Hôpital La Fontonne, Antibes — J.F. Dor; Hôpital Cochin, Paris — F. Dreyfus; Clinique Saint Jean, Brussels, Belgium — C. Dubois; Clinique de Chaumont, Chaumont — G. Dupont; Centre Val d'Aurelle, Montpellier — M. Fabbro; Hôpital J. Monod, Le Havre — C. Fruchart; Clinique les Fougères, Dieppe — J.P. Gaillard; Centre Hospitalier Universitaire de Rennes, Rennes — B. Grosbois; Centre René Huguenin, Saint-Cloud — M. Janvier; Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland — N. Ketterer; Centre Hospitalier du Val de Sambre, Sambreville, Belgium — C. Leroy; Clinique Saint Pierre, Ottignies, Belgium — M. Maerevoet; Hôpital des Canaux, Macon — F. Marechal; Hôpital Saint Joseph, Gilly, Belgium — P. Mineur; Hôpital Saint Joseph, Arlon, Belgium — P. Pierre; Centre Hospitalier Universitaire Nord, Marseilles — G. Sebahoun; Centre Hospitalier de Meaux, Meaux — C. Soussain; and Hôpital Nord, Amiens — C. Traulle.

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