

Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte

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We report the outcome of patients included in the LNH-98.5 study, which compared cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) to rituximab plus CHOP (R-CHOP) therapy in 399 patients with diffuse large B-cell lymphoma (DLBCL) aged 60 to 80 years, with a median follow-up time of 10 years. Clinical event information was updated in all living

patients (with the exception of 3 patients) in 2009. Survival end points were improved in patients treated with R-CHOP: the 10-year progression-free survival was 36.5%, compared with 20% with CHOP alone, and the 10-year overall survival was 43.5% compared with 27.6%. The same risk of death due to other diseases, secondary cancers, and late relapses was observed in both

study arms. Relapses occurring after 5 years represented 7% of all disease progressions. The results from the 10-year analysis confirm the benefits and tolerability of the addition of rituximab to CHOP. Our findings underscore the need to treat elderly patients as young patients, with the use of curative chemotherapy. (*Blood*. 2010; 116(12):2040-2045)

Introduction

The addition of rituximab to the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen has greatly improved outcomes for patients with diffuse large B-cell lymphoma (DLBCL), the most frequently occurring subtype of non-Hodgkin lymphomas.¹ The first randomized study comparing the standard CHOP chemotherapy regimen to CHOP plus rituximab (R-CHOP) was the LNH-98.5 trial, performed by the Groupe d'Etudes des Lymphomes de l'Adulte (GELA).^{2,3} These initial findings were obtained after a median follow-up period of 2 years, and demonstrated that the addition of rituximab to the CHOP regimen resulted in favorable outcomes in elderly patients with DLBCL, with a greater proportion of complete responders and longer event-free and overall survival compared with CHOP alone. The 5-year follow-up results have confirmed these initial findings.⁴ Since then, several other randomized studies have shown the benefits of this treatment regimen in DLBCL as well as in other B-cell lymphoma subtypes.⁵⁻⁹

The R-CHOP treatment regimen confers 2 major benefits: (1) a decrease in the number of patients with disease progression during treatment (refractory patients), and (2) a decrease in the number of relapsing patients. Thus, R-CHOP therapy results in a decrease in the number of patients with an event, a longer period of time before disease progression, and a longer overall survival in this patient population.

Here, we present an analysis of the patients included in the LNH-98.5 study with a median follow-up period of 10 years. No

plateau was reached with the main survival end points; some late relapses occurred. Our results demonstrate that the benefits of R-CHOP therapy are maintained over this 10-year period.

Methods

Patients

Eligibility criteria for enrollment in the LNH-98.5 study were the following: age 60 to 80 years, with previously untreated DLBCL according to the World Health Organization classification,¹⁰ stage II, III, or IV disease, and performance status (PS) 0 to 2 according to the Eastern Clinical Oncology Group (ECOG) scale. Exclusion criteria included the following: T-cell lymphoma, previous history of indolent lymphoma, central nervous system or meningeal involvement, a history of active cancer during the previous 5 years, any serious active concomitant disease, or if, in the opinion of the investigator, the patient's general condition was not suitable for the administration of 8 courses of CHOP therapy. Patients with a cardiac contra-indication to doxorubicin (abnormal contractility on echocardiography), or a neurologic contra-indication to vincristine were also excluded from the study. In addition, patients with positive serology for HIV or a history of unresolved hepatitis B virus infection (defined by the presence of HBs antigen, or HBc antibody without HBs antibody) were excluded. Patient enrollment was based upon the diagnosis of CD20-positive DLBCL at each study center; however, each diagnosis was independently confirmed by a central pathology review panel consisting of at least 3 hematopathologists. This study was fully compliant with all provisions of the Declaration

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of Helsinki and was conducted according to Good Clinical Practice guidelines. The study protocol was approved by the institutional review boards or ethics committees of all participating centers, and all patients provided written informed consent prior to enrolment in the study.

The baseline characteristics of the 399 patients included in our study population were identical across both study arms, and have been described in previous publications.^{3,4} Median age was 70 years and is now 80 years, with the oldest patient being 91 years old. Only 20% of the patients had localized stage; 31% had a tumor larger than 10 cm; 66% had elevated lactate dehydrogenase levels; and the age-adjusted International Prognostic Index (aIPI) score was 2 or 3 in 60% of the patients.

Staging consisted of clinical examination, thoracic and abdominal computed tomography (CT) scans, blood counts, measurements of lactate dehydrogenase and β_2 -microglobulin serum levels, bone marrow biopsy, electrocardiogram, echocardiography in patients with a history of cardiac disease or in patients older than 75 years, and cerebrospinal fluid examination in patients with bone marrow infiltration or head and neck involvement, or if otherwise clinically indicated.

Randomization and treatment

Patients were centrally randomized to treatment with either CHOP or R-CHOP after stratification according to study center and aIPI scores (0 or 1 vs 2 or 3).¹¹ Patients treated with CHOP received 750 mg/m² cyclophosphamide, 50 mg/m² doxorubicin, 1.4 mg/m² vincristine up to a maximum dose of 2 mg on day 1, and 40 mg/m²/day prednisone on days 1 to 5, for each treatment cycle. Patients underwent 1 cycle of treatment every 3 weeks, for a total of 8 cycles. Patients treated with R-CHOP received rituximab at a dose of 375 mg/m² on day 1 of each of the 8 cycles. Rituximab infusion was interrupted in the event of fever, chills, edema, mucosal congestion, hypotension, or any serious adverse event, and was resumed later. No complementary radiation therapy was planned for the treatment of bulky tumors or on persisting tumor masses at the end of treatment.

If a patient developed grade 4 neutropenia or febrile neutropenia after a cycle of CHOP or R-CHOP, all subsequent cycles were administered with granulocyte colony-stimulating factor (G-CSF) supportive therapy. When the onset of grade 4 neutropenia occurred alongside an infection despite G-CSF support, the doses of cyclophosphamide and doxorubicin were decreased by 50% for all the following cycles. If grade 4 neutropenia persisted, chemotherapy was discontinued. If a patient developed grade 3 or 4 thrombocytopenia, the doses of cyclophosphamide and doxorubicin were decreased by 50% for all the following cycles. If grade 3 or 4 thrombocytopenia persisted, chemotherapy was discontinued. If neutrophil levels were lower than 1.5 G/L or platelet levels lower than 100 G/L before a treatment cycle, the treatment was delayed for up to 2 weeks. If the patient's neutrophil and platelet counts did not rise above these levels after 2 weeks, chemotherapy was discontinued. For patients in the R-CHOP arm, rituximab treatment was also discontinued if CHOP therapy was stopped. Subsequent treatments for patients withdrawn from CHOP or R-CHOP therapy were administered at the discretion of the investigator.

Follow-up

Response to treatment was evaluated after 8 treatment cycles, or after stopping the planned treatment. Subsequently, clinical examination was performed every 3 months for the first 2 years, then every 6 months for the next 3 years, and thereafter at the discretion of the investigator. A thoracic and abdominal CT scan was performed after 3 months, then every 6 months during the first 2 years, and then annually for the following 3 years.

All the departments in which the patients were treated were contacted for the follow-up information. When necessary, the relevant information was obtained from the patients' private physicians or, in some cases, the patients or family members. All patients were updated for information on events in 2009 (July 1, 2009, was the cut-off date for patients still alive), with the exception of 3 cases where the last follow-up was at 14 months, 33 months, and 5 years. The median follow-up period was 10 years in both study arms.

Table 1. Number of events observed in the CHOP and R-CHOP arms after a 10-year median follow-up period

Type of event	CHOP	R-CHOP
PD during treatment	44 (22.3%)	19 (9.4%)
New unplanned treatment	9 (4.6%)	11 (5.4%)
Progression after stable disease	1 (0.5%)	1 (0.5%)
PD after partial response	5 (2.5%)	6 (3.0%)
Relapse for CR patients	71 (36.0%)	49 (24.3%)
Death without PD during treatment	12 (6.1%)	12 (5.9%)
Death without PD after treatment	16 (8.1%)	33 (16.3%)
No event	39 (19.8%)	71 (35.1%)

CHOP indicates cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHOP, rituximab-CHOP; PD, progressive disease; and CR, complete response.

Outcome measures

The primary efficacy parameter was event-free survival (EFS). Events were defined as the following: disease progression or relapse, initiation of a new (unplanned) anticancer treatment (eg, radiation therapy), or death from any cause without progression. Secondary efficacy end points included overall survival (OS), progression-free survival (PFS), disease-free survival (DFS), response rates, and toxicity. The definition of PFS was almost identical to that of EFS, with the exception that late deaths not related to the underlying lymphoma or its treatment were not considered treatment failures.¹² DFS only included patients who reached a complete response (CR) or undocumented CR (CRu) at the end of the treatment. EFS, PFS, and OS were calculated as the time from randomization to the date of the first reported event. DFS was calculated as the time from response assessment to the date of the first reported event. Patients with no reported event at the time of analysis were censored at the most recent assessment date. Tumor responses were classified as CR, CRu, partial response (PR), stable disease (SD), or progressive disease (PD) according to the criteria proposed by the International Workshop.¹² Survival in relapsing patients was defined as the duration from the first day of the new treatment to the time of death, or last visit.

Statistical analysis

The sample size was calculated to detect an increase in the 3-year EFS rate from 30% to 45%. It was estimated that 400 patients recruited over 3 years and followed for a minimum of 1 year would be required to provide 80% power at the overall 5% ($\alpha = .05$, 2-sided) significance level. One patient was not included in the final analysis because she withdrew consent.

EFS, PFS, DFS, and OS were analyzed using the log-rank test and expressed as Kaplan-Meier plots. Analyses of efficacy and safety followed the intent-to-treat principle and included all 399 patients randomized between August 1998 and March 2000. Statistical analyses were performed using SAS Version 9.1.3 software (SAS Institute) by the GELA statistical department. All *P* values given are 2-tailed.

Results

Previously published response rates for the R-CHOP and CHOP study arms were the following: 75% and 63% for CR and CRu, 8% and 6% for uncompleted responses (PR and SD), 9% and 22% for PD, and 6% in both arms for death during treatment, respectively ($P = .005$).^{3,4} Among the 197 patients treated with CHOP, 158 (80.2%) had an event, in comparison to 131 of the 202 patients (64.9%) treated with R-CHOP ($P < .0001$; Table 1).

A total of 204 patients had progressive disease, 124 (62.9%) in the CHOP arm and 80 (39.6%) in R-CHOP arm. Seventy-seven patients died without progressive disease, 31 (15.7%) in the CHOP arm and 46 (22.8%) in the R-CHOP arm. Among the 204 patients with progressive disease, 178 (87%) occurred during the first

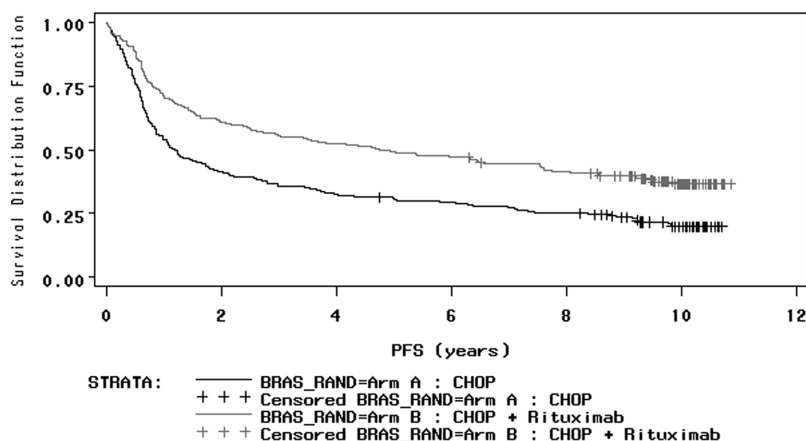


Figure 1. Progression-free survival in patients treated with CHOP and R-CHOP. Median progression-free survival (PFS) was 1.2 years (95% CI: .9-1.8) in the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) arm and 4.8 years (95% CI: 2.7-7.6) in the CHOP plus rituximab (R-CHOP) arm ($P < .0001$).

3 years of follow-up (90% in the CHOP arm and 83% in the R-CHOP arm), 12 (6%) during years 4 and 5 (5% in the CHOP arm and 8% in the R-CHOP arm), and 14 (7%) after 5 years (5% in the CHOP arm and 10% in the R-CHOP arm). Ten-year PFS was 20.1% (95% confidence interval [CI]: 14.6-26.2) in the CHOP arm and 36.5% (95% CI: 29.7-43.3) in the R-CHOP arm. Progression-free survival is depicted in Figure 1. PFS according to aaIPI score is presented in supplemental Figure 1 (available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article).

Two hundred fifty-two patients died, 140 (71.1%) in the CHOP arm and 112 (55.4%) in the R-CHOP arm. Causes of death in the CHOP and R-CHOP arms were lymphoma progression (68% and 56%, respectively), treatment toxicity (11% and 13%, respectively; only 2% in each arm due to infection), another cancer (9% in both arms), other diseases (11% and 21%, respectively) or unknown causes (1 and 3 patients, respectively). More patients died from causes unrelated to lymphoma or its treatment in the R-CHOP arm but no pattern emerged, as most of the underlying conditions related to the deaths were present before the diagnosis of DLBCL. Most of the causes were cardiovascular diseases, 10 in the CHOP arm and 16 in the R-CHOP arm. Ten-year OS was 27.6% (95% CI: 21.4-34.3) in patients treated with CHOP and 43.5% (95% CI: 36.4-51.4) in patients treated with R-CHOP. The OS is depicted in Figure 2. OS according to aaIPI score is presented in supplemental Figure 2.

For the assessment of disease-free survival, only patients with CR or CRu were included in the analysis: 10-year DFS was 42.6% (95% CI: 33.6-51.4) in the CHOP arm and 64.3% (95% CI: 55.4-71.9) in the R-CHOP arm. DFS is shown in Figure 3.

The prognosis for survival after disease progression is poor for most patients, regardless of the type of progressive disease. The median OS after progression was 0.6 and 0.7 months for the CHOP and R-CHOP arms, respectively. However, some patients responded well to salvage therapy and had a relatively long survival period after progression: the 5- and 10-year survival after progression were 14.6% and 10.5% in the CHOP arm, compared with 25.0% and 8.6% in the R-CHOP arm, respectively (Figure 4).

No standard salvage therapy was recommended in the study protocol; this was determined at the discretion of the investigator. Rituximab-containing salvage treatment regimens were not administered for early disease progressions, as the drug was not available in Europe outside the clinical trial setting during this time. However, most of the late relapses (those occurring after 2002) were treated with rituximab-containing chemotherapy. Overall, the number of patients exhibiting late disease progression was low, but there was a trend toward a better outcome for those patients treated with R-CHOP compared with those treated with CHOP alone (Table 2). The median age at time of progression was 72 years and did not influence the response to salvage therapy. In a multivariate analysis of parameters associated with long term survival after progression, only low aaIPI score (0 or 1) and long duration of PFS (longer than 1 year) were statistically found to be associated with a longer survival after progression ($P < .001$ in both cases). No difference was observed between the 2 arms (rituximab or not in first line).

Forty-three patients (10.8%) developed another cancer after entering the study, 22 in the CHOP arm and 21 in the R-CHOP arm. Twenty-eight of these patients died, 16 in the CHOP arm, with death being secondary to the second cancer in 12 patients, and 12 in

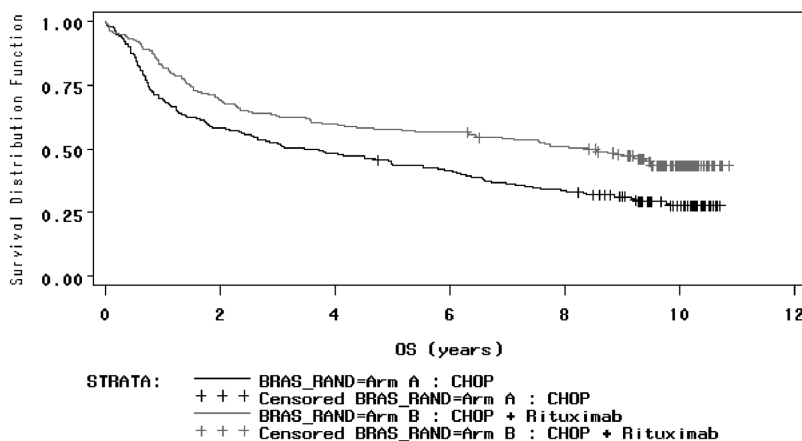
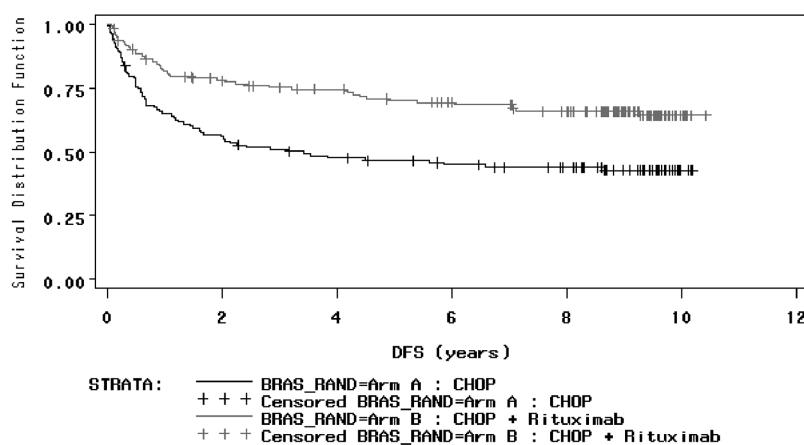


Figure 2. Overall survival in patients treated with CHOP and R-CHOP. Median overall survival (OS) was 3.5 years (95% CI: 2.2-5.5) in the CHOP arm and 8.4 years (95% CI: 5.4-not reached) in the R-CHOP arm ($P < .0001$).

Figure 3. Disease-free survival in patients treated with CHOP and R-CHOP. Median disease-free survival (DFS) was 3.4 years (95% CI: 1.6-not reached) in the CHOP arm and was not yet reached (95% CI: not reached-not reached) in the R-CHOP arm ($P < .0001$).



the R-CHOP arm, with death being secondary to the second cancer in 10 patients. Three patients developed a third cancer, 1 in the CHOP arm and 2 in the R-CHOP arm, so a total of 46 cancers were observed in 43 patients after entering the study. There was no pattern in the type of secondary cancers that occurred: myelodysplasia or acute myeloid leukemia was observed in 2 patients in each arm. The most frequently observed solid tumors in the CHOP and R-CHOP arms were in the lung (7 and 4, respectively), colon (3 and 4, respectively), prostate (3 and 2, respectively), breast (3 and 1, respectively) and bladder (0 and 2, respectively). All other cancers were present in 1 patient (kidney, melanoma, multiple myeloma, ovary, liver, pleura, head and neck, esophagus, skin epidermoid, and 1 of unknown origin).

Discussion

The 10-year follow-up results from the LNH-98.5 trial, the first randomized study comparing the standard CHOP regimen to R-CHOP, confirm the benefits of adding rituximab to CHOP for the treatment of patients with DLBCL. The addition of rituximab improved PFS and OS rates in this patient population, with an overall increase of 16% versus CHOP alone. This difference was even more pronounced in patients exhibiting CR at the end of treatment (22%).

The patient cohort chosen for this trial was elderly DLBCL patients (60-80 years of age), a particularly challenging group to manage and treat. With the improvements in PFS and OS rates from the addition of rituximab to standard treatment regimens, a

significant proportion of elderly patients experience long-term survival. At 10 years, more than 40% of the patients in our study were alive and in first CR. This emphasizes that the goal of treatment in elderly patients, as in younger patients, should be the cure of the lymphoma.

No plateau was reached for any of the survival end points as shown in Figures 1 and 2. This is explained by the late relapses and death from other causes (either related or unrelated to the lymphoma or its treatment) in this relatively elderly group of patients. The higher mortality rate found in our study is likely due to the advanced age of the patient population. Currently, the median age of our patient cohort is 80 years. This is an old group of patients in which other diseases have been observed (often related to the cause of death), even taking into account the increasing median age of the standard population over the past 50 years. We observed a high risk of death due to cardiovascular diseases or secondary cancers; in general, these are the most frequent causes of death in this age group. We did not observe a higher occurrence of any cause of death or development of secondary cancer in the R-CHOP arm compared with the CHOP arm. Secondary cancers developed in our patient population and were the cause of death in more than half of the cases. Again, we did not observe a trend in favor of higher risk in the R-CHOP group, nor in the increased occurrence of any subtype of secondary cancer. In general, the number of patients with secondary cancer is not higher than expected, given the age of the patient population.

Late relapses are not often described in studies on patients with DLBCL. However, it is important to note that the median follow-up time in most reported studies is usually limited to 5 years or less. If

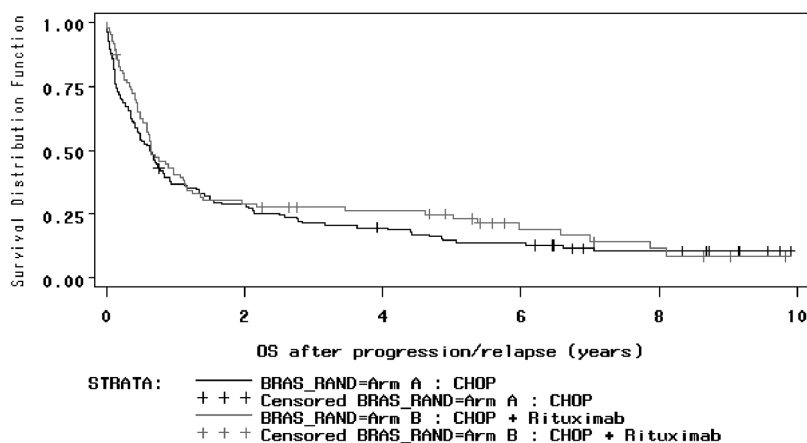


Figure 4. Survival after disease progression in patients initially treated with CHOP or R-CHOP. P not significant.

Table 2. Outcome of patients with PD according to time of progression and initial treatment arm

	Median survival (y)	2-year survival (%)	3-year survival (%)	5-year survival (%)
PD within the first 3 years				
CHOP	0.6	25.9	19.6	14.3
R-CHOP	0.6	18.2	18.2	16.7
PD between years 4 and 5				
CHOP	3.0	83.3	50.0	16.7
R-CHOP	not reached	83.3	66.7	66.7
PD after 5 years				
CHOP	0.9	22.2	22.2	22.2
R-CHOP	not reached	87.5	87.5	58.3

PD indicates progressive disease; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; and R-CHOP, rituximab-CHOP.

more than 80% of the progressions occurred before 3 years, 6% occurred during years 4 and 5, and 7% after 5 years. We did not plan to rebiopsy all patients with relapses, and due to the age of our patient population, very few patients underwent a new biopsy at the time of progression. Therefore, we do not know whether some of the relapses that occurred were indolent lymphomas. However, a separate study in relapsing DLBCL patients who underwent a new biopsy at the time of relapse did not reveal a large proportion of indolent lymphomas at relapse.¹³ In this study in young and elderly patients, 4% of relapses were observed after 5 years. In the present study, the rate of relapses is slightly higher (7% compared with 4%). This may be a secondary consequence of the greater age of the patients. Indeed, we had previously described a tendency toward higher relapse rates in elderly patients.¹⁴ In the present study, these late relapses were observed in both treatment groups and were slightly higher in the R-CHOP arm (10% compared with 5% in the CHOP arm). However, this observation is counterbalanced by the markedly greater risk of early relapses occurring in the CHOP arm.

As is usually seen in DLBCL, patient outcome after disease progression is poor, with 70% of the patients dying from lymphoma within the first 2 years after progression. However, our results suggest that a small proportion of patients may be salvaged and can survive for a relatively long period (Figure 4). Indeed, there is a trend in favor of a survival advantage in the R-CHOP group (Table 2). These results do not support those of the Collaborative Trial in Relapse Aggressive Lymphoma (CORAL) study that showed that relapsing young DLBCL patients previously treated with R-chemotherapy have a lower PFS than those not having received rituximab in first line.¹⁵ The fact that most patients who progressed after R-CHOP have late relapse may explain this discrepancy. Thus, whenever possible, elderly patients should be offered the best treatment to eradicate the underlying disease at the time of progression.

In conclusion, our results demonstrate that the benefits of the addition of rituximab to CHOP chemotherapy for DLBCL patients persist over a 10-year follow-up period. Late relapses can be expected in DLBCL patients if the follow-up period is sufficiently long. However, the risk of death due to other diseases or secondary cancers was not higher in the R-CHOP group. These findings confirm that the use of R-CHOP can improve patient outcomes in elderly DLBCL patients, and that the beneficial effects are sustained over a long follow-up period.

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Authorship

Contribution: B.C. designed the research, analyzed and interpreted data, and wrote the manuscript; and C.T., E.V.D.N., G.L., I.P., S.C., S.L., G.M., M.M., C.S., K.B., D.B., C.F., and H.T. collected data and reviewed the manuscript.

Conflict-of-interest disclosure: B.C. served on an advisory board, participated in a speaker's bureau, and received research funding from Roche. H.T. participated in a speaker's bureau for Roche. The remaining authors declare no competing financial interests.

For a complete list of Groupe d'Etudes des Lymphomes de l'Adulte participants, see the supplemental Appendix.

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