Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study

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The FL2000 study was undertaken to evaluate the combination of the anti-CD20 monoclonal antibody rituximab with chemotherapy plus interferon in the first-line treatment of follicular lymphoma patients with a high tumor burden. Patients were randomly assigned to receive either 12 courses of the chemotherapy regimen CHVP (cyclophosphamide, adriamycin, etoposide, and prednisolone) plus interferon-α2a (CHVP+I arm) over 18 months or 6 courses of the same chemotherapy regimen combined with 6 infusions of 375 mg/m^2 rituximab and interferon for the same time period (R-CHVP+I arm). After a median follow-up of 5 years, event-free survival estimates were, respectively, 37% (95% confidence interval [CI], 29%-44%) and 53% (95% CI, 45%-60%) in the CHVP+I and R-CHVP+I arm (P = .001). Five-year overall survival estimates were not statistically different in the CHVP+I (79%; 95% CI, 72%-84%) and R-CHVP+I (84%; 95% CI, 78%-84%) arms. In a multivariate regression analysis, event-free survival was significantly influenced by both the Follicular Lymphoma International Prognostic Index score (hazard ratio = 2.08; 95% CI, 1.6%-2.8%) and the treatment arm (hazard ratio = 0.59; 95% CI, 0.44%-0.78%). With a 5-year follow-up, the combination of rituximab with CHVP+I provides superior disease control in follicular lymphoma patients despite a shorter duration of chemotherapy. This study's clinical trial was registered at the National Institutes of Health website as no. NCT00136552. (Blood. 2008; 112:4824-4831)

Introduction

Follicular lymphoma is the second most common lymphoma in adults and patients, with adverse prognostic features usually considered to be incurable with chemotherapy alone. The use of immunotherapy has been advocated for a long time, and several randomized trials have demonstrated the benefit of α-interferon when combined with chemotherapy.[1,2] Although other studies have been unable to confirm these results,[3-6] a recent meta-analysis indicates that α-interferon does improve overall survival (OS) of follicular lymphoma patients, especially when used in combination with anthracycline-containing chemotherapy regimens and at sufficient doses.[7] Long-term results of the GELF86 study, which evaluated a low-dose anthracycline combination chemotherapy regimen given for 12 courses over 18 months with interferon, indicate that this combination produces long-term remissions.[8] This regimen was not found to be inferior to other approaches, such as fludarabine alone[9] or myeloablative therapy supported with autologous stem cell transplantation.[10,11] However, no chemotherapy regimen, with or without interferon, for first-line therapy of follicular lymphoma patients has been clearly established as a standard regimen worldwide. Moreover, despite the relatively long

survival of patients with follicular lymphoma, their prognosis may diverge according to patient and disease characteristics. An international index was therefore developed to assess patient prognosis. Based on 5 simple independent risk factors (hemoglobin < 12 g/dL, serum lactic dehydrogenase > upper normal value, Ann Arbor stage III-IV, nodal sites > 4, age > 60 years), the Follicular Lymphoma International Prognostic Index (FLIPI) enabled separation of patients with 0 or 1 adverse factor with a 5-year survival estimate of 91% from those with 3 or more adverse factors with a 5-year survival estimate of 53%.[12]

Monoclonal antibodies directed against the CD20 antigen, expressed on B-cell lymphoma cells, have been developed in the past years, and the humanized anti-CD20 antibody rituximab has demonstrated its efficacy as a single agent in follicular lymphoma.[13-15] Results from 3 randomized trials[16-18] have indicated that combined rituximab with chemotherapy can improve the outcome of follicular lymphoma patients. In addition, earlier in vitro and in vivo data have shown that interferon may enhance the activity of monoclonal antibody, probably by mobilizing immune effector cells.[19,20] Phase 2 studies also suggest that interferon can improve the efficacy of

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rituximab in follicular lymphoma patients by increasing the quality or duration of response compared with rituximab alone.[21,22]

The Groupe d'Etude des Lymphomes de l'Adulte (GELA) and the Groupe Ouest Est des Leucémies et Autres Maladies du Sang (GOELAMS) therefore undertook the FL2000 randomized study to evaluate the benefit of the combination of rituximab in follicular lymphoma patients. It was hypothesized that the benefit of rituximab introduction could be substantial and therefore chosen to decrease the number of chemotherapy courses in the rituximab-containing experimental arm. This report presents the FL2000 final analysis with a 5-year median follow-up.

Methods

Study design

The FL2000 was an open randomized multicenter study (Document S1, available on *Blood* website; see the Supplemental Materials link at the top of the online article). The primary endpoint, event-free survival (EFS), was used to calculate the sample size of the study. To detect a change at 3 years of 20% (null hypothesis, 50%; alternative hypothesis, 70%) with the rituximab-containing experimental arm, we calculated that 360 patients would be required to provide the study with 90% power at an overall 5% significance level. The secondary endpoints were toxicity, response rate, and OS.

The study management was operated by the GELA coordinating center that issued treatment allocation after confirmation of patient eligibility. Case report forms were sent to the GELA and GOELAMS coordinating center and keyed in twice for verification. Outliers and erroneous values were checked routinely. Queries and on-site monitoring were used for final validation. No interim analysis was done.

The protocol was approved by the local or national ethics committees and the national regulatory agency according to the French and Belgium laws. Patients were required to give written informed consent before being included in the study in accordance with the Declaration of Helsinki. The study was registered at the National Institutes of Health website as no. NCT00136552.

Patients

The study included untreated patients from 18 to 75 years of age with a histologic diagnosis of follicular lymphoma (grade 1, 2, or 3a) performed in the last 3 months on a lymph node biopsy. Patients were required to have Ann Arbor stage II, III, or IV disease and to fulfill at least any one of the following criteria for high tumor burden[2,10]: (1) presence of a bulk tumor defined by either one of the following: tumor lesion with a largest diameter greater or equal than 7 cm, spleen enlargement with a craniocaudal diameter greater than 20 cm, existence of 3 lymph nodes in 3 distinct nodal areas with a diameter greater or equal than 3 cm, pleural effusion, ascites, or symptomatic compressive syndrome; (2) presence of B symptoms (fever, night sweats, or weight loss); (3) a performance status on the Eastern Cooperative Oncology Group scale greater than 1; or (4) elevated serum levels of lactic dehydrogenase (above normal values) or β2-microglobulin ($\geq$ 30 mg/dL). Patients with contraindications to anthracyclines, interferon, or rituximab, with known positivity for HIV or active viral hepatitis, or with a previous malignancy were not eligible for the study. Although the index was not established at that time, all parameters used to define the FLIPI were also measured at registration. Pathologic review of the biopsy material was performed after inclusion by a panel of 3 expert pathologists.

Treatments

The control arm, designated as CHVP+I (cyclophosphamide, adriamycin, etoposide, and prednisolone, plus interferon-α2a), consisted, as in previous studies, of 12 courses of the CHVP regimen administered every 28 days for 6 courses and then every 56 days for an additional 6 courses combined with

18 months of interferon. Each CHVP course included 600 mg/m^2 cyclophosphamide intravenously on day 1, 25 mg/m^2 doxorubicin intravenously on day 1, 100 mg/m^2 etoposide intravenously on day 1, and 40 mg/m^2 prednisolone orally from day 1 to day 5. α2a-Interferon was administered subcutaneously during 18 months 3 times a week at an initial dose of 4.5 million units (MU) per injection for patients younger than 70 years or 3 MU per for patients older than 70 years.

The experimental arm, designated as R-CHVP+I, essentially included 2 modifications to this control arm. First, 6 infusions of rituximab (375 mg/m^2) were administered: to take advantage of the putative synergy between rituximab and interferon, the first antibody administration was delayed until 2 months of interferon exposure (at the time of the third course of chemotherapy). Moreover, to complete the administration of rituximab infusions during the first 6 months of treatment, 2 infusions of the antibody were administered with the third and fourth CHVP courses (on day 1 and 8) and then the 2 others with each of the fifth and sixth courses. The second modification consisted of a reduced number of CHVP cycles, with only 6 courses every 28 days, whereas interferon was delivered at the same doses during 18 months.

No dose reduction of chemotherapy was planned or allowed, but a CHVP course could be delayed for 7 days if the absolute neutrophil count was less than 1.5 g/L or the platelet count was less than 100 g/L. The dose of interferon could be also adapted to 3 mU per injection (1.5 mU for patients 70 years and older) in case of neutropenia or excessive fatigue, and the drug could be interrupted for 7 days in case of grade 4 neutropenia persisting after appropriate dose reduction. Prophylactic acetaminophen was recommended before each injection of interferon.

Evaluation of response and follow-up

After an initial staging, including CT scan of the chest, abdomen, and pelvic areas, and a bone marrow biopsy, the evaluation of response was performed after 6 chemotherapy courses (6 months) and at the end of the whole treatment (18 months). Disease evaluation for response assessments was recommended in the International Workshop criteria.[23] Complete response (CR) 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 (CRu) was defined as a CR with the persistence of some radiologic abnormalities, which had to have regressed in size by at least 75%. Partial response (PR) was defined as the regression of all measurable lesions by more than 50%, the disappearance of nonmeasurable lesions, and the absence of new lesions. Stable disease was defined as a regression of any measurable lesion by 50% or less or no change in 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%, or growth of any measurable lesion that had regressed during treatment by more than 50% from its smallest dimensions.

Responding patients with previous bone marrow involvement for which bone marrow evaluation was missing at evaluation were considered has having a PR even if they met the criteria of CRu or CR. Any residual marrow infiltrate that could not be demonstrated to be a reactive infiltrate using immunostaining was considered as a positive bone marrow biopsy, and the response, if other criteria were met, as a PR.

Patients who completed their treatment had a complete clinical examination every 3 months for the first year and then every 6 months for 5 years. A CT scan was performed yearly, and a new bone marrow biopsy was performed 18 months after treatment completion or when clinically indicated. Toxicity was assessed using the National Cancer Institute of Canada (NCIC) Toxicity Scale.[24]

Statistics

All analyses were performed on an intention-to-treat basis. Patient characteristics and complete remission rates were compared by the χ^2 and Fisher exact tests. OS was measured from the date of randomization to death from any cause. EFS was measured from the date of randomization to that of disease progression, relapse, initiation of a new

Table 1. Detailed clinical and biological characteristics of the 358 patients constituting the study population of the FL2000 study

	Missing values	Number (%) CHVP+I	R-CHVP+I
Age > 60 years	–	96 (52)	89 (51)
Male sex	–	82 (45)	96 (55)
ECOG performance status > 1	–	16 (9)	11 (6)
B symptoms presence	1	52 (29)	38 (22)
Ann Arbor stage III or IV	2	165 (91)	152 (87)
Number of nodal sites involved > 4	–	78 (43)	86 (49)
Bone marrow involvement	4	121 (67)	108 (62)
Extranodal sites > 1	3	73 (40)	60 (35)
LDH more than upper normal value	5	66 (36)	64 (37)
Hemoglobin < 12 g/dL	2	30 (17)	37 (21)
β2-microglobulin > 3 mg/L	28	56 (33)	62 (38)
IPI score > 2	10	71 (39)	60 (36)
FLIPI 0-1 factors	9	37 (21)	28 (16)
FLIPI 2 factors	9	59 (33)	63 (37)
FLIPI 3 factors or more	9	83 (46)	79 (46)

The distribution of patient characteristics was not significantly different ($\chi^2 > 0.05$) between the 2 treatment groups. ECOG indicates Eastern Cooperative Oncology Group; IPI, International Prognostic Index[30]; and FLIPI, Follicular Lymphoma International Prognostic Index.

alternate treatment, or death from any cause. Duration of response was estimated from the day of response assessment until relapse, progression, or death from any cause. Survival functions were estimated by the Kaplan-Meier method and compared by the log-rank test. Differences between the results of comparative tests were considered significant if the 2-sided *P* value was less than 0.05. Because the FL2000 trial was not stratified by the FLIPI, we checked for effects of prognostic factors on outcome resulting from sampling fluctuation in the treatment groups using multivariate analysis of survival. The Cox regression model included FLIPI and treatment as explanatory variables. The interactions between risk factors and treatment were also included in the model. All *P* values are 2-tailed. Statistical analyses were performed with SAS 913 software (SAS Institute, Cary, NC).

Results

Characteristics of patients

From May 2000 until May 2002, 360 patients were registered in 54 centers in France and Belgium. One patient withdrew his consent after registration, and one patient had a major inclusion violation (registered at relapse). Therefore, 358 patients were analyzed: 183 patients in the CHVP+I arm and 175 in the R-CHVP+I arm. The median age was 61 years (range, 25-75 years). The majority of patients (89%) had advanced stage disease (Ann Arbor

stage > II) and several adverse prognostic parameters (Table 1). This was reflected by the distribution of patients according to the FLIPI score: 65 (19%) patients were in the low-risk index (0 or 1 factor) category, 122 (35%) patients in the intermediate-risk (2 factors), and 162 (46%) patients in the high-risk category (3 factors or more). No differences were observed in the distribution of these characteristics between the 2 treatment groups (Table 1). A central pathologic review was performed for 344 cases (96%): 4 diagnoses of follicular lymphoma could not be formally confirmed resulting from technical problems, whereas 12 cases were classified as nonfollicular lymphoma subtypes.

Treatment tolerance

Among patients who did not progress during therapy, 153 (98%) and 161 (98%) of the patients received the planned chemotherapy courses during the first 6 months in the CHVP+I and R-CHVP+I arms, respectively. In the CHVP+I arm, 116 (87%) of 134 patients without death or progression received the 6 planned cycles of chemotherapy consolidation.

Overall, very limited life-threatening toxicity was observed in each study arm (Table 2). Although neutrophil toxicity of grade 3 or more was frequently encountered in each arm during the induction period, this was not associated with severe infections. During the consolidation, neutrophil toxicity was more frequent in patients receiving CHVP+I as opposed to those receiving R-CHVP+I.

In total, 237 (66%) patients followed the interferon treatment according to the protocol, with dose adaptation (45 patients) or short (less than 4 weeks) interruptions (55 patients), without significant differences in adaptation between the 2 study arms (not shown). In addition, interferon treatment was stopped in 50 patients resulting from disease progression (CHVP-I arm, 31 cases and R-CHVP-I arm, 19 cases, respectively) and was interrupted either for more than 1 month (16 cases) or definitively (72 cases) resulting from toxicity. These major interruptions were observed in 47 patients in the CHVP+I arm and 41 patients in the R-CHVP+I arm.

Response to treatment

At the end of the 6-month induction treatment period, 92 (26%) of the patients achieved a CR and 80 (22%) a CRu, 148 (41%) patients were in PR, 11 (3%) had stable disease, whereas 26 (7%) had progressed and 1 died without documented lymphoma progression (Table 3). There was a marked difference (global χ^2 for all response strata, *P* < .001) in the response quality according to each treatment arm (Table 3), with significantly more patients achieving a CR or a CRu in the R-CHVP+I arm (63% vs 34%; *P* < .001). Conversely, more patients experienced treatment failure in the CHVP+I arm. With another year of treatment, including, respectively, 6 courses of chemotherapy plus interferon in the CHVP+I

Table 2. Major grade 3 and 4 organ toxicities (NCIC scale) observed in 358 patients in the FL2000 study

	Induction (first 6 months of treatment) Number (%)		Consolidation (additional 12 months) Number (%)	
Grade 3-4 toxicities	CHVP+I	R-CHVP+I	CHVP+I	R-CHVP+I
Neutrophil	114 (62)	103 (59)	69 (38)	11 (6)*
Hemoglobin	9 (5)	6 (3)	4 (2)	1 (1)
Platelets	6 (3)	5 (3)	4 (2)	2 (2)
Fever	2 (1)	2 (1)	1 (1)	0 (0)
Infection	0 (0)	4 (2)	2 (1)	2 (1)
Cardiac	3 (2)	2 (2)	1 (1)	0 (0)

No significant differences in terms of grade 3 or 4 toxicities were observed between the 2 treatment arms except for neutrophil toxicity.
*P < .001.

Table 3. Assessment of response to treatment

Response to treatment	At 6 months		At 18 months	
	Number (%)		Number (%)	
	CHVP+I	R-CHVP+I	CHVP+I	R-CHVP+I
Complete response	29 (16)	63 (36)	71 (39)	90 (51)
Unconfirmed complete response	33 (18)	47 (27)	20 (11)	28 (16)
Partial response	94 (51)	54 (31)	40 (22)	24 (14)
Stable disease	9 (5)	2 (1)	3 (2)	1 (1)
Disease progression	18 (10)	8 (5)	47 (26)	31 (18)
Death	0 (0)	1 (1)	2 (1)	1 (1)
P value	<.001		=.035	

Assessment of response to treatment after 6 and 18 months, respectively, of therapy observed in 358 patients in the FL2000 study in each study arm. The actual number of patients with each response status is reported with the percentages according to the whole study population. The P value was obtained using a global χ^2 test for all strata.

arm and interferon only in the R-CHVP+I arm, there was an overall improvement in the quality of response in both arms (global χ^2 for all response strata, $P = .035$) (Table 3). At 18 months, 50% versus 67% of the patients were, respectively, in CR or CRu in the CHVP+I and R-CHVP+I arm ($P = .001$).

Patient outcome

This analysis was performed with a censor date set at October 1, 2006, with follow-up information for 99% of the patients being alive at this date. The median follow-up for all patients was 5 years (range, 0.2-6.4 years). Of 358 patients, 190 had progressed or relapsed and 11 died without prior documented disease progression. The median EFS was 2.9 years in patients who received CHVP+I and was not reached for those who received R-CHVP+I. Five-year EFS estimates (Figure 1A) were, respectively, 37% (95% confidence interval [CI], 29%-44%) and 53% (95% CI, 45%-60%) in the CHVP+I and R-CHVP+I arm ($P = .001$). To assess the outcome of those patients who responded after completion of the whole treatment, the response duration in patients who were in CR, Cru, or PR at 18 months of treatment was analyzed. Indeed, the response duration was significantly different ($P = .012$) between the 2 treatment arms, with respective 4-year estimates of 44% (95% CI, 32%-54%) versus 64% (95% CI, 55%-72%) in the CHVP+I and R-CHVP+I arms, respectively (Figure 1B). Finally, the 5-year OS of patients receiving CHVP+I was 79% (95% CI, 72%-84%) versus 84% (95% CI, 78%-84%) in those that received R-CHVP+I (Figure 1C). Those results were essentially similar in the 328 patients with confirmed follicular lymphoma after central pathologic review (not shown).

The FLIPI score allowed separation of the whole study population into 3 different risk categories (Figure 2), with significantly different outcome for each group both for 5-year EFS and OS ($P < .001$, for each). When the low- and intermediate-risk groups were considered together and compared with the poor-risk group, this index was also able to discriminate risk groups for patients in each treatment arm (not shown). When considering together the 187 patients who presented either a low or an intermediate FLIPI score, no significant difference in outcome was observed according to each treatment arm (Figure 3A,B). However, the outcome of the 162 patients with the highest FLIPI score (3-5 adverse prognostic factors) was found to be significantly different both for 5-year EFS ($P = .001$) and OS ($P = .025$) between the CHVP+I- and R-CHVP+I–treated patients (Figure 3C,D).

Cox regression analysis, including the FLIPI score (low and intermediate vs high) and the treatment arm, confirmed the impact of both parameters for EFS (respectively, FLIPI: hazard ratio [HR] = 2.08; 95% CI, 1.6-2.8; and R-CHVP+I treatment:

HR = 0.59; 95% CI, 0.44-0.78) and OS (respectively, FLIPI: HR = 4.11; 95% CI, 2.34-7.23; and R-CHVP+I: HR = 0.67; 95% CI, 0.41-1.11).

Discussion

This randomized trial compared the efficacy of 12 courses of chemotherapy plus interferon with only 6 courses of chemotherapy combined with rituximab and interferon. The results demonstrate that patients receiving the combination of rituximab plus chemotherapy and interferon achieved more rapidly and more frequently a response to chemotherapy, as outlined by the CR and CRu rates observed at 6 and 18 months in each respective treatment arm. In addition, with a 5-year follow-up, significantly fewer events (HR = 0.59) were observed in patients treated with R-CHVP+I. However, OS was not significantly improved for those patients, although the survival of patients in both arms appeared to be favorable at 5 years. Indeed, the 5-year OS probability for patients in the FL2000 in the different FLIPI prognostic subgroups (low, intermediate, and high) was found to be, respectively, 95%, 89%, and 70% as opposed to 91%, 78%, and 53% in the original index publication.[12]

These results demonstrate that the combination of rituximab with chemotherapy plus interferon improves the outcome of follicular lymphoma patients with a high tumor burden. They are in line with the reports from other studies (Table 4), which have shown improved response rate and progression-free survival when rituximab was combined with other chemotherapy regimens in the first-line treatment of follicular lymphoma patients.[16-18] The present analysis performed with a long follow-up confirms that the response duration is also significantly prolonged with the R-CHVP+I combination. Although the rituximab infusions were administered during the first 6 months of treatment, the benefit obtained with this combined treatment appears to last at least 4 years after these infusions: approximately two-thirds (64%) of the patients responding to therapy at the end of treatment did not experience disease progression at this time. The lack of OS difference for the whole population of patients with a long-term follow-up is probably related to the efficacy of salvage treatments (frequently containing anti-CD20 monoclonal antibodies) in patients who experienced progression (not shown).

As an exploratory analysis, the outcome of patients was examined according to their clinical characteristics and the number of adverse factors using the FLIPI score, which was described after the completion of the trial. This index was able to discriminate distinct groups of patients both for EFS and OS in the control as
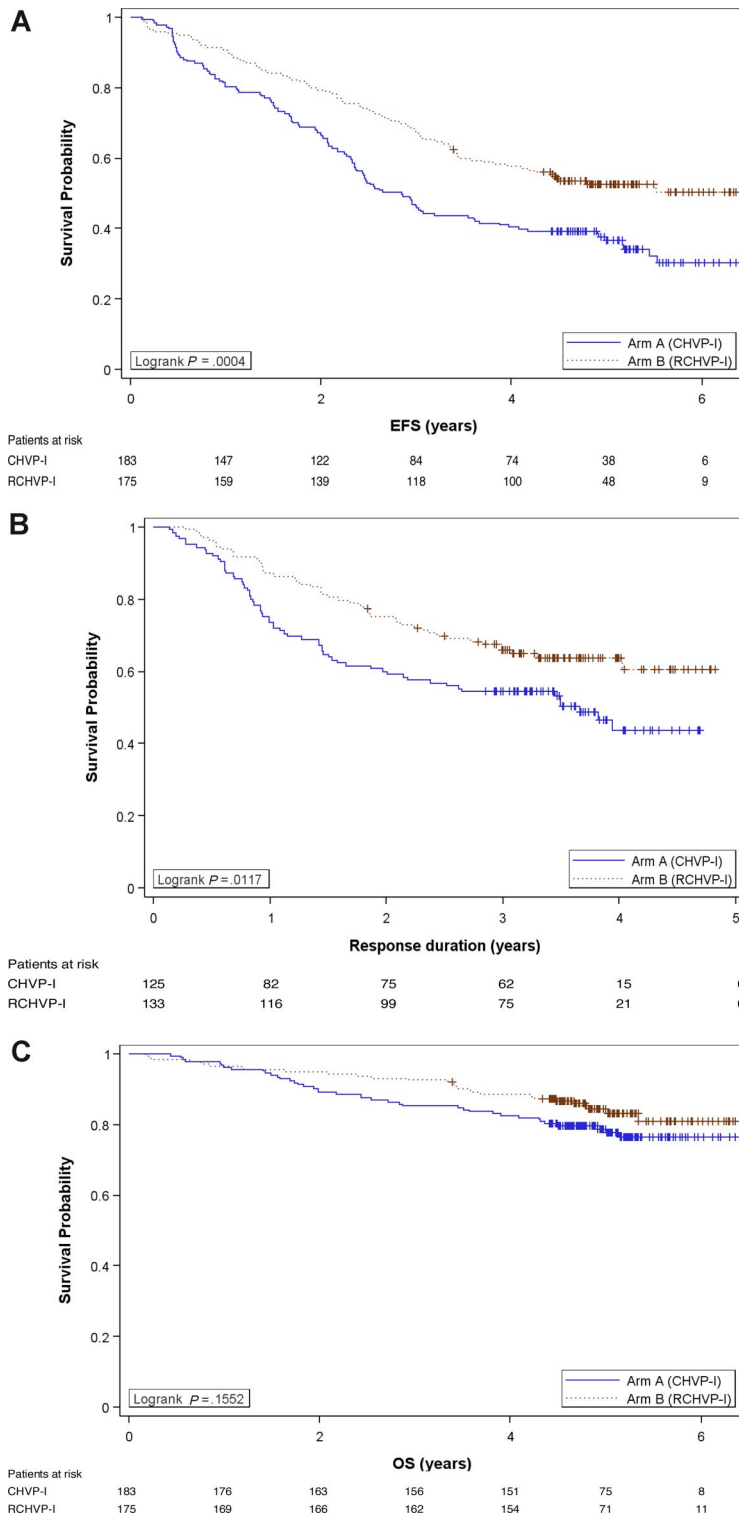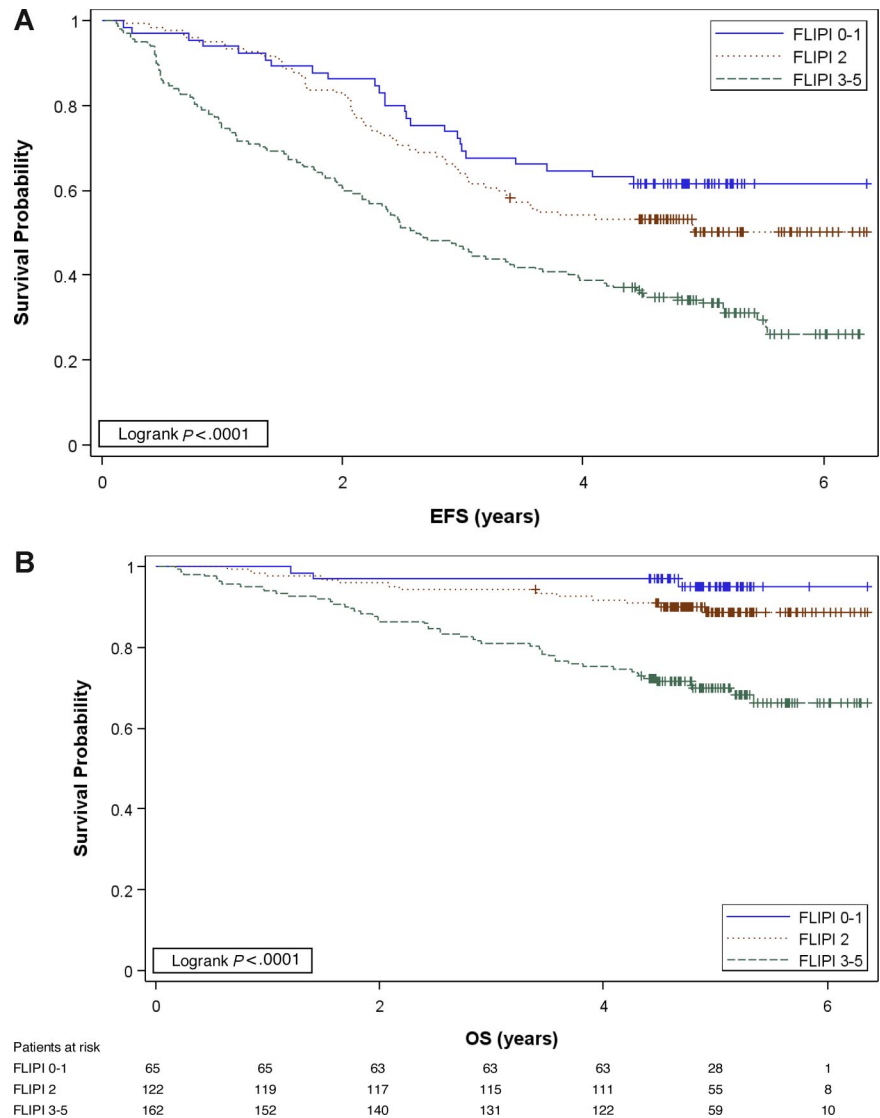
Figure 1. Outcome of the 358 patients in the FL2000 study with a 5-year median follow-up. (A) Event-free survival. (B) Response duration from the end of treatment (for 258 of 273 responding patients with a confirmed date of response evaluation). (C) Overall survival. Arm A (CHVP+I): blue solid line; Arm B (R-CHVP+I): dotted red line.

well as in the experimental arm. When the effect of treatment was analyzed for these different groups, the addition of rituximab did not appear to significantly influence the outcome of patients in the more favorable FLIPI groups, whereas patients with 3 to 5 adverse prognostic factors gained a significant benefit from this combination both in terms of EFS and OS.

Indeed, the backbone regimen used in this study is different from others that either did not contain anthracyclines[16] or used consolidation with autologous transplantation[17] or interferon until disease progression.[18] The control arm CHVP+I appears to provide reproducibly a good control of the disease[8,10] with a median time to progression close to 3 years. This may contribute to the lack of significant outcome difference observed in good prognosis patients in this study. Of note, the results observed using CHVP+I without rituximab are identical to those observed when rituximab is combined with the CVP (cyclophosphamide, vincristine, prednisone) regimen,[16] where patient characteristics were similar to those of the current study (Table 4).

Figure 2. Outcome of the 358 FL2000 patients according to the FLIPI score. FLIPI 0-1 indicates 0 or 1 adverse factor (blue solid line); FLIPI 2, 2 adverse factors (red dotted line); and FLIPI 3-5, 3 to 5 adverse factors (green dashed line). (A) Event-free survival. (B) Overall survival.

Patients at risk						
FLIPI 0-1	65	65	63	63	63	28	1
FLIPI 2	122	119	117	115	111	55	8
FLIPI 3-5	162	152	140	131	122	59	10

Indeed, with a proportion of patients in the different FLIPI risk groups that does not markedly differ from study to study (Table 4), these results also seem to parallel those observed in other trials, where a significant survival benefit was observed for either the whole population or the high-risk FLIPI group. The superiority of the rituximab combination while 6 instead of 12 courses of chemotherapy are administered is noteworthy. The respective contribution of the low-dose anthracycline combination or of the 18-month duration of interferon administration together with rituximab is difficult to determine. The alleged synergistic effect of interferon in enhancing rituximab activity may be reflected by the duration of response observed after R-CHVP+I administration. However, the study design is unable to demonstrate that the benefit of rituximab observed here is

Table 4. Randomized studies in follicular lymphoma patients using a combination of rituximab plus chemotherapy

Treatment	Patients within each FLIPI strata (% with low/intermediate/high risk, respectively)	Median age, y	Estimated % PFS in the experimental arm	Median PFS, m		Overall survival %	
				Control arm	Experimental arm	Control arm	Experimental arm
CVP versus R-CVP[16,31]	19/41/40	52	50 (at 3 years)	15	34	77 (at 4 years)	83* (at 4 years)
CHOP versus R-CHOP†[17]	14/41/45	55	80 (at 2 years)	31	not reached	90 (at 2 years)	95* (at 2 years)
MCP versus R-MCP‡[18]	7/37/56	59	71 (at 4 years)	26	not reached	74 (at 4 years)	87* (at 4 years)
CHVP+I versus R-CHVP+I	19/35/46	61	53 (at 5 years)	35	not reached	79 (at 5 years)	84 (at 5 years)

CHOP indicates cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; PFS, progression-free survival; ASCT, autologous stem cell transplantation; IFN, interferon; MCP, mitoxantrone, chlorambucil, prednisone; and R-MCP, rituximab, mitoxantrone, chlorambucil, prednisone.

*P value for difference in overall survival significant.

†CHOP or R-CHOP was followed by ASCT or IFN.

‡MCP and R-MCP were followed by IFN consolidation.

§CHVP combined with IFN: 12 chemotherapy courses in the control arm versus 6 in the rituximab-containing arm.
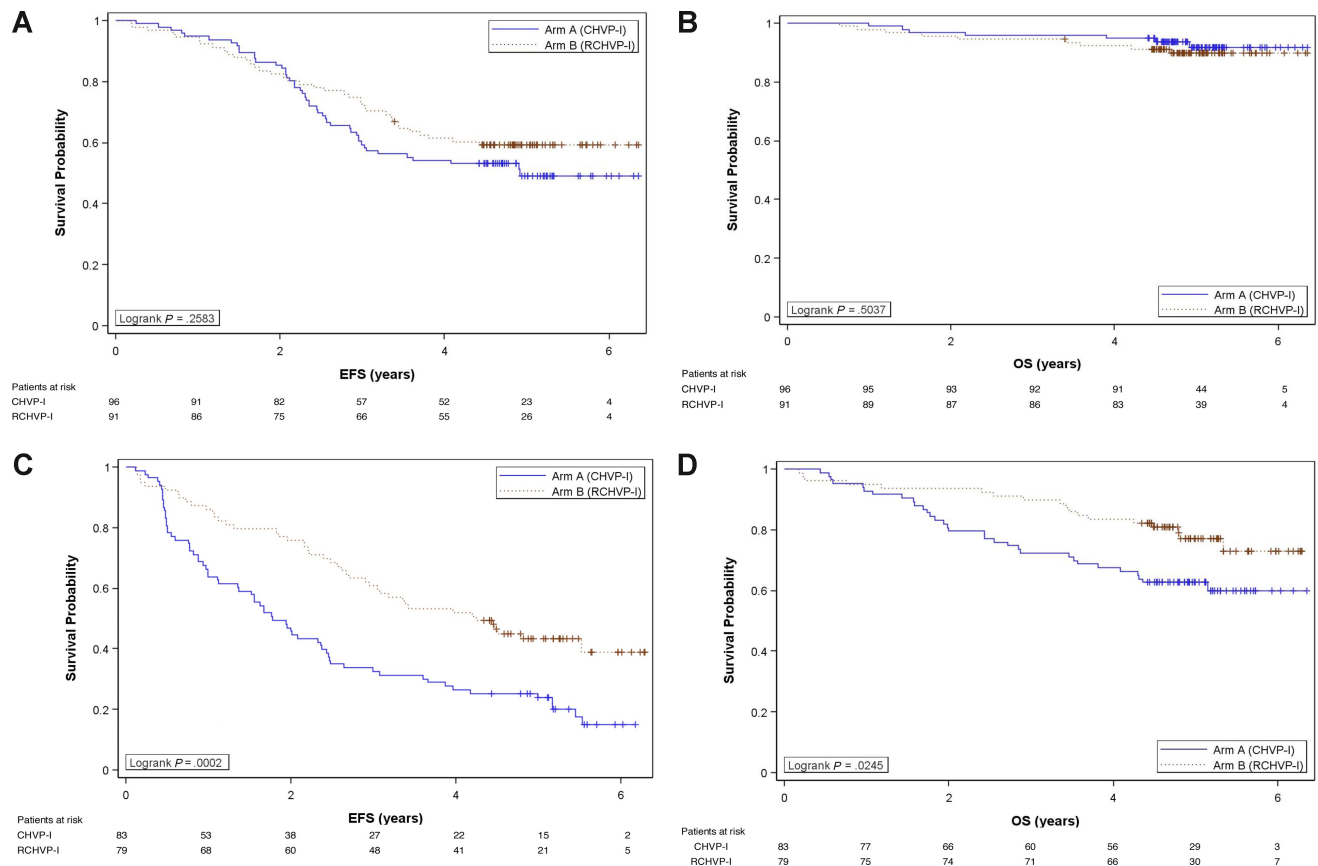
Figure 3. Outcome of the follicular lymphoma in the 2 treatment arms according to the different groups defined by the FLIPI. (A) Event-free survival in low- and intermediate-risk FLIPI patients. (B) Overall survival in low- and intermediate-risk FLIPI patients. (C) Event-free survival in high-risk FLIPI patients. (D) Overall survival in high-risk FLIPI patients. Arm A (CHVP+I): blue solid line; Arm B (R-CHVP+I): dotted red line.

superior to that observed without interferon in other studies. The toxicity of the first 6 months of treatment was not different between the 2 arms of the study, whereas interferon was better tolerated during the 12-month consolidation period in the R-CHVP+I arm. These results therefore support the possibility that the addition of rituximab to a standard chemotherapy-based treatment may allow reduction of the duration of the CHVP+I treatment.

However, this 5-year follow-up analysis also indicates that the rituximab and CHVP+I combination probably does not provide a cure for follicular lymphoma patients, especially in poor prognosis patients in whom a steadily constant rate of events during the first 4 years is observed. This continuous risk of relapse observed here and in other trials underlines the need to improve the therapeutic strategies in those patients. The reproducible benefits observed with rituximab[25] appear to go beyond the advantage that was observed with interferon[7]; and until any benefit of the combination of both forms of immuno-therapy has been eventually shown, the use of rituximab combination with chemotherapy had become a new standard. Other approaches, such as radio-immunotherapy[26] or mainte-nance with monoclonal antibodies,[27,28] recently appear promis-ing in increasing or prolonging the responses obtained with chemotherapy alone or with rituximab. The current Primary Rituximab and Maintenance (PRIMA) study (NCT00140582[29]) is then currently testing 2 years of rituximab maintenance in patients responding to rituximab plus chemotherapy as a way to further improve the outcome of follicular lymphoma patients.

Authorship

Contribution: G.S., N.M., P.B., J.-F.R., and C. Foussard provided study concept and design; G.S., S.d.G., F.M., C. Doyen, J.-F.R., C.H., P.B., B.M., R.B., B.A., C. Fermé, C. Dartigeas, P.F., C.S., L.X., and C. Foussard provided study materials or patients and reviewed the data; G.S., N.M., L.X., and C. Foussard analyzed and interpreted data and wrote the manuscript; and all authors gave final approval of the manuscript.

A complete list of FL-2000 study clinical investigators and center participants can be found in Document S1, available on the *Blood* website; see the Supplemental Materials link at the top of the online article.

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