Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial

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ABSTRACT

A previous pilot study with rituximab, gemcitabine and oxaliplatin showed promising activity in patients with refractory/relapsed B-cell lymphoma. We, therefore, conducted a phase II study to determine whether these results could be reproduced in a multi-institutional setting. This phase II study included 49 patients with refractory (n=6) or relapsing (n=43) diffuse large B-cell lymphoma. The median age of the patients was 69 years. Prior treatment included rituximab in 31 (63%) and autologous transplantation in 17 (35%) patients. International Prognostic Index at enrollment was >2 in 34 patients (71%). The primary endpoint was overall response rate after four cycles of treatment. Patients were planned to receive eight cycles if they reached at least partial remission after four cycles. After four cycles 21 patients (44%) were in complete remission and 8 (17%) in partial remission, resulting in an overall response rate of 61%. Factors significantly affecting overall response rate were early (<1 year) progression/relapse (18% *versus* 54%; *P*=0.001) and prior exposure to rituximab (23% *versus* 65%; *P*=0.004). Five-year progression-free and overall survival rates were 12.8% and 13.9%, respectively. Rituximab, gemcitabine and oxaliplatin were well tolerated with grade 3-4 infectious episodes in 22% of the cycles. These results are the first confirmation from a multicenter study that rituximab, gemcitabine and oxaliplatin provide a consistent response rate in patients with refractory/relapsed diffuse large B-cell lymphoma. This therapy can now be considered as a platform for new combinations with targeted treatments. *This trial was registered at clinicaltrial.gov under #NCT00169195.*

Introduction

The addition of rituximab to conventional chemotherapy has improved response, event-free and overall survival rates in patients with diffuse large B-cell lymphoma (DLBCL). However, some patients are refractory to initial treatment or relapse after achieving a response. Disease relapse and refractory disease both constitute significant challenges for the treatment of lymphoma, particularly for patients with advanced age or significant comorbidities, who are consequently not candidates for high-dose consolidative therapy. Patients with DLBCL who have an early relapse - less than 12 months after ending first-line treatment - or relapse after prior rituximab based-treatment have a poor prognosis. In a single-center pilot study, the R-GemOx regimen, a combination of rituximab, gemcitabine and oxaliplatin, showed promising activity with an acceptable toxicity profile.[1] The Lymphoma Study Association (LYSA) conducted a phase II multicenter study to prospectively evaluate the R-GemOx regimen in an homogeneous series of patients with relapsed/refractory DLBCL who were not candidates for high-dose therapy.

Methods

Study design

This study was an open label, single-arm, multicenter phase II trial. It was deposited on the US National Institutes of Health website (NCT00169195). The primary endpoint was the overall response rate after completion of four cycles of treatment (ORR). We anticipated an ORR rate of 55% and computed that an average sample of 50 patients would provide 80% power at the overall 5% (two-sided) significance level to detect a complete response rate above 40% (null hypothesis: 40%, alternative hypothesis: 55%).[2] In accordance with French regulatory laws, the local ethics committees and the national regulatory agency approved the protocol. All patients provided written informed consent to participation in the study which complied with all the provisions of the Declaration of Helsinki and its current amendments and was carried out in accordance with good clinical practice guidelines.

Selection of patients

The multicenter study phase II study of R-GemOx enrolled patients in ten institutions in France between August 2003 and January 2009. Patients were eligible if they were aged between 18 and 75 years old

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The results were partly presented in an oral session at the American Society of Hematology annual meeting in Chicago, USA, in December 2010.
The online version of this article has a Supplementary Appendix.
Manuscript received on April 25, 2013. Manuscript accepted on June 10, 2013.
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and had refractory/relapsed CD20-positive DLBCL that had been diagnosed in accordance to the World Health Organization (WHO) classification at the time of enrollment. Patients were required to be: (i) in first or second relapse, (ii) previously treated with a chemotherapy regimen containing anthracycline, with or without rituximab, and (iii) not eligible for high-dose therapy.

Chemotherapy and dose adjustments

R-GemOx was administered as previously described.[1] Rituximab 375 mg/m^2 was administered on day 1 and gemcitabine and oxaliplatin at the doses of 1000 mg/m^2 and 100 mg/m^2, respectively, on day 2. Cycles were repeated every 15 days. Eight cycles were planned if patients reached at least a partial response after four cycles. No dose adjustment was planned in the event of hematologic toxicity, but cycles were postponed until the absolute neutrophil count reached 1.0x10^9/L and the platelet count reached 100x10^9/L. The dose of oxaliplatin was adjusted in the event of peripheral neuropathy, as previously described.[1]

Staging and follow up

The extent of the disease was assessed by physical examination, relevant laboratory tests, computed tomography (CT-scan) of the chest, abdomen, and pelvis, cerebrospinal fluid examination, bone marrow biopsy, and other investigational procedures depending on clinical symptoms. Lymphomas were classified in accordance with criteria of the WHO classification.[3] Thoracic, abdominal, and pelvic CT scans and bone marrow biopsy were conducted to assess response according to the International Working Group Criteria after four and eight cycles.[4]

Statistical methods

The ORR was defined as the rate of complete responses, unconfirmed complete responses and partial responses. The relative dose intensity for gemcitabine and oxaliplatin was calculated according to Hryniuk *et al.*[5] Survival curves were estimated using the product-limit method of Kaplan–Meier and compared using the log-rank test. Multivariate analysis was performed by a Cox model regression. All statistical analyses were performed using SAS software (SAS, version 9.2, SAS institute, Cary, NC, USA)

Biomarkers

Pathological specimens from 36 out of 49 patients (73%) with histological material available either at diagnosis (n=23) or at relapse (n=26) or in both situations (n=13) were more extensively analyzed in order to classify tumor biopsies according to cell of origin into germinal center B-cell like (GCB) *versus* non-GCB subtypes using CD10, BCL6 and MUM1 markers as previously published by Hans *et al.*[6]

Further details on the design and methods of this study are available in the *Online Supplementary Appendix*.

Results

Clinical characteristics and outcome

Figure 1 shows the consort diagram of the study. Forty-nine patients were enrolled and 48 were eligible for analysis. The non-eligible patient was under tutelage. The baseline characteristics of the 49 enrolled patients are shown in Table 1. Their median age was 69 years (range, 41 to 77 years). Prior treatments included doxorubicin in all the treated patients (100%), rituximab in 31 (63%) and high-dose therapy in 17. Forty-two patients (86%) were refractory to treatment or in first relapse and 22 patients (46%) relapsed less than 1 year after the end of last treatment. All

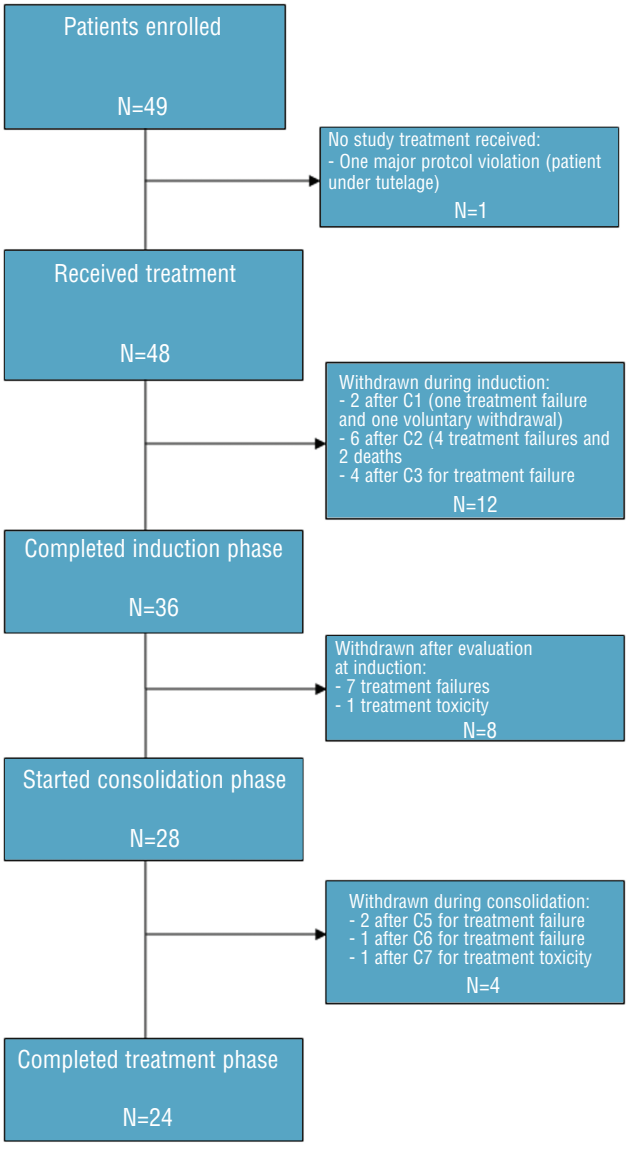

Figure 1. Flow chart of the patients in the study.

the patients had been treated at first line with a CHOP (n=33) or ACVBP (n=15) regimen combined with rituximab in 28 patients. After this first-line treatment, 81% had achieved complete remission, 6% had had a partial response, and 12% had progressive disease. Before enrollment in the present study, six out of seven patients were treated for a first relapse, with DHAP in four cases, CHOP in one case and ICE in another case, with rituximab in four patients. Seventeen patients previously received high-dose consolidative chemotherapy followed by autologous stem cell transplantation, 13 during their first-line treatment, and four at first relapse.

After completion of the pathological review, the diagnosis of DLBCL at relapse was confirmed in all the reviewed cases and the following subtypes were observed: DLBCL, not otherwise specified in 23 cases, DLBCL with follicular lymphoma in two and T-cell/histiocyte-rich DLBCL in one case. Considering the cases assessable for cell of origin, eight cases (35%) were classified, based on Hans's algorithm, as GCB and 15 cases (65%) as non-GCB subtype

for the primary cases (n=23). As regards the relapsed cases (n=26), ten cases (38%) were classified as GCB and 16 (62%) as non-GCB.

Response to treatment

As shown in Table 2, 29/48 patients achieved at least partial remission after four cycles of induction therapy. The ORR was 61% [95% confidence interval (95% CI): 45-74] with a complete response/unconfirmed complete response rate of 44%. It was affected by early (< 1 year) relapse/progression (36% *versus* 81%, *P*<0.0001). After four cycles of consolidation therapy, among the 29 responding patients, 18/21 patients remained in complete remission/unconfirmed complete remission, four of eight remained in partial remission and seven patients progressed. The ORR at the end of treatment was 46% (95% CI: 31%-61%) and the complete response/unconfirmed complete response rate was 38% (95% CI: 24%-53%). The median duration of response was 10 months. The ORR was affected by refractory disease/relapse <1 year (18% *versus* 69%, *P*=0.0004) and also by prior rituximab treatment (32% *versus* 71%, *P*=0.01). The impact of GCB *versus* non-GCB subtype on ORR was not statistically significant (69 *versus* 41%, *P*=0.11) in this limited series.

A CT scan review was performed in 80% of the cases. As there was no discrepancy between the interpretation of the local readers and the experts (*data not shown*), the central review had no impact on the present analysis.

Survival

At the data cutoff point, February 1, 2011, the median follow-up was 65 months. Among the 48 patients who received at least one cycle of treatment, 12 patients received fewer than four cycles and 24 completed the entire treatment (see Trial profile in Figure 1). The 5-year progression-free survival rate was 13% (95% CI: 5% to 24%; median, 5 months) while the 5-year overall survival rate was 14% (95% CI: 6% to 26%; median, 11 months) (Figure 2). The median progression-free survival was adversely affected by prior rituximab treatment (4 months *versus* 11 months, *P*=0.02), early (<1 year) relapse (3 months *versus* 10 months, *P*=0.04), but not significantly by the secondary age-adjusted International Prognostic Index (Saa-IPI) (5 months *versus* 9 months, *P*=0.07). The median overall survival was also affected by early relapse (6 months *versus* 23 months, *P*=0.03), Saa-IPI (8 months *versus* 39 months; *P*=0.01) and prior rituximab treatment (8 months *versus* 27 months, *P*=0.02). Prior autologous stem cell transplantation also had a significant effect (5 months *versus* 22 months, *P*=0.03). In multivariate analysis, the only significant prognostic factor for overall survival was the Saa-IPI (hazard ratio =3.0, *P*=0.01).

The non-GCB/GCB phenotype was not predictive of the outcome, being associated with 5-year progression-free survival rates of 10% and 23%, respectively (*P*=0.31) and 5-year overall survival rates of 10% and31%, respectively (*P*=0.37) (Figures 3 and 4).

Treatment and toxicity

The overall number of cycles administered was 273 (range per person, 1-8). No dose reduction was required for rituximab or gemcitabine. Based on data collected from the population who received the first four cycles, (36 patients) the median received dose intensities of oxaliplatin, gemcitabine and rituximab were 92.5%, 93.3% and 91.6%, respectively, of the theoretical dose. Importantly, 24 patients (50%) completed the planned eight cycles. The most common toxicities during treatment were hematologic with 98% of patients developing low neutrophil counts, including 73% with grade ≥3 neutropenia on at least one occasion. Ninety-two percent of patients experienced platelet toxicity, including 44% who had at least one grade 3 episode. Grade 3 and 4 neutropenia was reported in 31% and 42% of cycles, respectively, while grade 3 and 4 thrombocytopenia was reported in 23% and 21% of the cycles, respectively. During the treatment period, 16 patients (33%) received at least one red blood cell transfusion, and 11 patients (23%) received at least one platelet transfusion. Eighteen patients developed grade 2 neurotoxicity and four patients developed grade 3 neurotoxicity leading to a dose reduction of oxaliplatin. Two patients did not receive the fourth cycle and in one patient the seventh and eighth cycles of consolidation were administered without oxaliplatin because of significant neurotoxicity. Grade 3 renal toxicity was observed in only one patient and febrile neutropenia was reported in only 4% of cycles. Finally, a total of 26 serious adverse events were experienced by 19 patients (40%). These events required hospitalization or prolongation of hospitalization.

Table 1. Patients' characteristics.

Number of patients	49
Sex	
Male	27 (55)
Female	22 (45)
Age (years) [median (range)]	69 (41-77)
< 60	15 (31)
> 60	34 (69)
Performance status	
0-1	38 (78)
≥ 2	11 (22)
Stage	
I or II	6 (12)
III or IV	43 (88)
Lactate dehydrogenase	
Elevated (>1xnormal)	37 (76)
Normal	12 (24)
Saa-IPI score	
Low or low/intermediate (0-1)	12 (24)
High or high/intermediate (2-3)	37 (76)
Extranodal site > 1	25 (51)
Saa-IPI score	
0-1	15 (31)
2-3	34 (69)
Bone marrow involvement	8 (17)
Large cells	6 (12)
Small cells	1 (2)
Median time from last treatment to R-GemOx treatment (months)	14 (1-130)
Duration of last remission	
≥ 1 year	22 (46)
< 1 year	26 (54)
Disease status	
Primary refractory	6 (12)
First relapse	36 (74)
Second relapse	7 (14)

Saa-IPI score: secondary age-adjusted International Prognostic Index score. R-GemOx: rituximab, gemcitabine and oxaliplatin.

Causes of deaths

Forty (83%) of the patients (83%) had died by the time of the analysis, most of whom due to lymphoma (90%). The other causes of death were thrombotic microangiopathy which occurred 1 week after the seventh cycle and was considered as probably related to gemcitabine in one patient (3%), concurrent illness (myocardial infarction) in one patient (3%), and other reasons (accidental drowning and neurological deterioration) in two patients (5%).

Discussion

In this phase II study in 48 patients with relapsed DLBCL, four cycles of the R-GemOx regimen were associated with an ORR of 61% with a complete response/unconfirmed complete response rate of 44%. This ORR was superior to the anticipated threshold of 55% retained to define the sample size on the basis of our previous pilot study.[1] The regimen was associated with a low toxicity profile characterized mostly by the low rate of febrile neutropenia and the excellent dose intensity. The population of the present study was highly selected since all the enrolled patients were not eligible for transplantation, mainly because of advanced age or previous high-dose therapy. The data are in line with those from previous phase II trials demonstrating increased disease control from salvage chemotherapy with the addition of rituximab to ICE or DHAP. The recently published CORAL study compared the R-DHAP and R-ICE regimens in patients with relapsed/refractory DLBCL, which provided comparable ORR of 62.8 and 63.5%, respectively.[8] The ORR of the R-GemOx regimen reported here is similar to that observed in a relapsed, significantly younger popula-

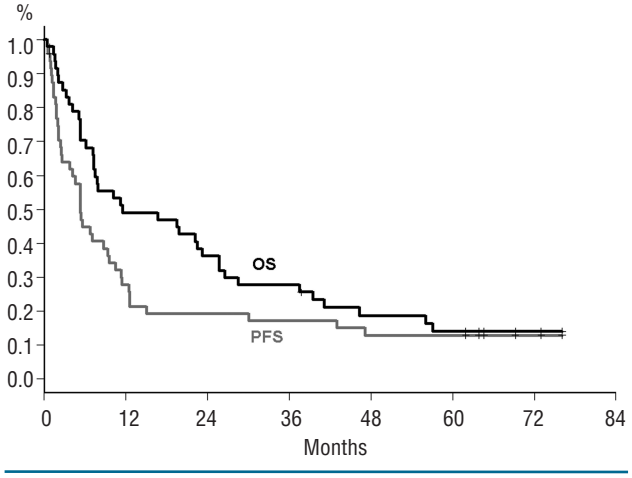

Figure 2. Overall survival (OS) and progression-free survival (PFS) in patients treated with R-GemOx.

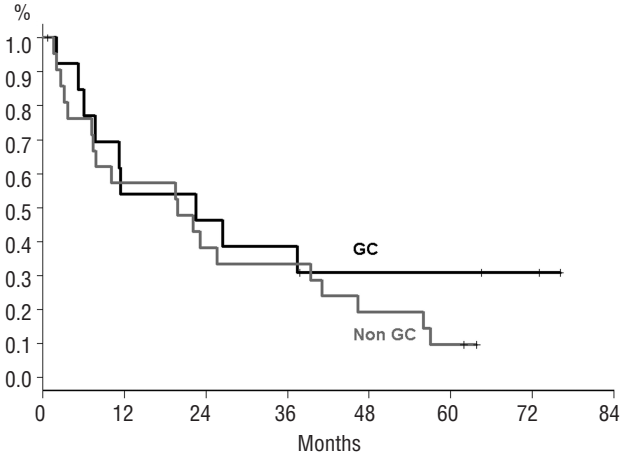

Figure 3. Overall survival according to pathological subtype of lymphoma.

Table 2. Response after R-GemOx induction treatment according to patients' characteristics.

Characteristics	N. of patients (%) CR/Cru	PR	SD	ORR (%)	PD	*P*	Total n.
All	11/10 (44)	8 (17)	5 (10)	61	14 (29)		48
Prior high-dose therapy							
Yes	3/0 (17)	4	1	41	2	0.05	17
No	8/10 (58)	4	1	71	3		31
Prior treatment with rituximab							
Yes	7/6 (42)	4 (13)	3 (10)	55	11(35)	0.29	31
No	4/4 (48)	4 (24)	2 (12)	71	3 (18)		17
Duration of response to last treatment							
< 1 year	2/2 (18)	4 (18)	4 (18)	36	10 (45)	0.002	22
> 1 year	9/8 (66)	4 (15)	1 (4)	81	4 (15)		26
Saa IPI							
0-1	3/1 (33)	3 (25)	2 (17)	58	3 (25)	0.90	12
2-3	8/9 (47)	5 (14)	3 (8)	61	11(31)		36
Saa IPI							
0-2	3/1 (27)	3 (20)	3 (20)	47	5 (33)	0.19	15
3-5	8/9 (51)	5 (15)	2 (6)	66	9 (27)		33
Subtype							
GC	3/5 (61)	3	0	84	1	0.11	13
Non-GC	6/4 (45)	3	1	59	3		22

CR: complete response; CRu: unconfirmed CR; PR: partial response; SD: stable disease; ORR: overall response rate; PD: progressive disease, GC germinal center. Saa-IPI score: secondary age-adjusted International Prognostic Index score.

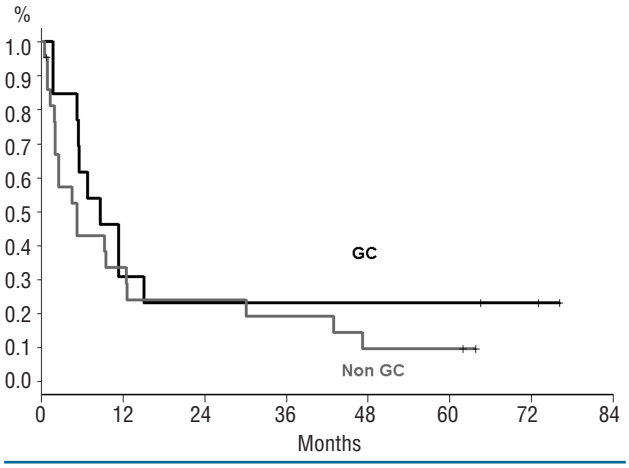

Figure 4. Progression-free survival according to pathological subtype of lymphoma.

tion of transplant-eligible patients. The toxicity profile of the R-GemOx regimen reported here, with only one case of grade 3 renal toxicity, appears to be more favorable than that reported for R-DHAP. The toxicity of R-GemOx was similarly low in a population of 46 relapsed patients who were heterogeneous regarding histology and number of previous lines of treatment, extending the experience with this regimen.[1] However 5-year progression-free and overall survival rates remain poor because of early disease progression, especially when relapse occurs less than 1 year from the initial diagnosis. Importantly, Corazelli *et al.* also reported the results of a trial using GemOx with (n=30) or without rituximab (n=32) in relapsed/refractory patients with different B-cell malignancies. They confirmed good response rates with an ORR of 78% and a complete response rate of 50% for patients treated with R-GemOx, with mainly hematologic toxicity.[9]

As in the CORAL trial, the cell of origin was not found to be a prognostic marker for second-line treatment of DLBCL. In this series of the 35 evaluable cases, we did not evidence a prognostic impact of the cell of origin phenotype according to Hans' algorithm. However, the trial was not powered to find differences in this variable. We also lack data concerning patients with double- or triple-hit DLBCL. As these hypothesis-generating data are crucial in the present treatment-targeted era, a retrospective study of a large sample population is now ongoing within all LYSA trials from the last 10 years.

Each component of the R-GemOx regimen may contribute to the regimen's efficacy; indeed, these results support a synergistic or supra-additive action of rituximab when combined with gemcitabine and oxaliplatin. Gemcitabine and oxaliplatin display supra-additive effects in human colon cancer cell lines, and the feasibility and safety of this combination has been demonstrated in various solid tumors and in patients with lymphoma.[10,11] Given that the toxicity profile of oxaliplatin is more favorable than that of cisplatin, studies have been conducted to investigate the substitution of oxaliplatin for cisplatin used in the standard DHAP regimen. The dexamethasone, cytarabine and oxaliplatin (DHAOx or DHAX) regimen has been assessed by three different study groups, demonstrating response rates of 50% to 73% in patients with advanced lymphoma.[12-14] Treatment was associated with frequent (66% - 75%) but manageable grade 3/4 hematologic toxicity. The lack of renal toxicity observed with oxaliplatin-containing regimens is particularly advantageous when treatment is considered in heavily pretreated patients or in elderly patients with comorbidities.

These results compare favorably with those of other combinations of rituximab and chemotherapy in the relapsed or refractory setting: Kewalramani *et al.*[15] reported a 78% ORR and 53% complete response rate in a population of 36 younger patients treated with rituximab, ifosamide, carboplatin and etoposide, none of whom had been previously exposed to rituximab. Jermann *et al.*[16] reported a 68% ORR and a 28% complete response rate to a regimen consisting of rituximab, etoposide, doxorubicin, vincristine, cyclophosphamide and prednisolone in a population of 50 patients among whom only 4% had received prior rituximab.

Novel single-agent therapies have shown anti-lymphoma activity in relapsed/refractory DLBCL.[17] Enzastaurin, a PKC beta inhibitor was well-tolerated and associated with prolonged progression-free survival in a small subset of patients with relapsed or refractory DLBCL.[18] The 28% ORR to lenalidomide in a study of 108 patients confirmed previous reports. Single-agent mammalian target or rapamycin (mTOR) inhibitors also showed significant activity: 30% ORR for everolimus,[19] 28% ORR for temsirolimus.[20] Finally, inotuzumab ozogamicin, an antibody targeting the CD22-antigen, which is linked to calicheamicin, provides an ORR of 15%.[21] The combination of rituximab and CMC544 was tested in a phase II study in follicular, diffuse large B-cell and refractory lymphoma in first or second relapse following initial treatment. The ORR in patients relapsing later than 6 months after previous therapy for DLBCL were as high as 72% and responses lasted for a median of 17 months.[22]

According to our data the major target population for the R-GemOx regimen might be unfit and/or elderly patients, for whom no meaningful therapeutic options can be found. A phase II study to evaluate whether the addition of enzastaurin can enhance the efficacy of R-GemOx in patients with relapsed DLBCL or transformed indolent lymphoma has been conducted.[23] The same study also evaluated the efficacy and safety of maintenance treatment with enzastaurin in patients who had not progressed after the combination therapy. More recently, the LYSA launched a multicenter phase trial Ib/II single arm study of inotuzumab ozogamicin plus rituximab alternating with R-GemOx in patients with CD20 and CD22 positive DLBCL in relapse or refractory after first- or second-line treatment, who are not candidates for autologous transplantation (NCT01562990).

Funding

Groupe d'Etudes des Lymphomes de l'Adulte, Sanofi, Lilly, and F Hoffmann La Roche.

Acknowledgments

We thank the staff of the LYSA-RC for the management of this work.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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