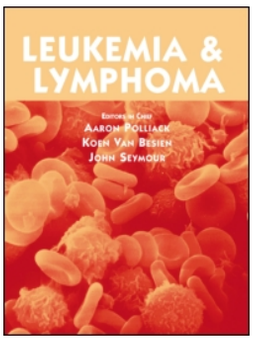

Leukemia & Lymphoma

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

Rituximab plus gemcitabine and oxaliplatin (R-GemOx) in refractory/relapsed diffuse large B-cell lymphoma: a real-life study in patients ineligible for autologous stem-cell transplantation

Clarisse Cazelles, Karim Belhadj, Hélène Vellemans, Vincent Camus, Elsa Poullot, Philippe Gaulard, Liana Veresezan, Emmanuel Itti, Stéphanie Becker, Muriel Carvalho, Jehan Dupuis, Fabien Le Bras, François Lemonnier, Louise Roulin, Taoufik El Gnaoui, Fabrice Jardin, Nicolas Mounier, Hervé Tilly & Corinne Haioun

To cite this article: Clarisse Cazelles, Karim Belhadj, Hélène Vellemans, Vincent Camus, Elsa Poullot, Philippe Gaulard, Liana Veresezan, Emmanuel Itti, Stéphanie Becker, Muriel Carvalho, Jehan Dupuis, Fabien Le Bras, François Lemonnier, Louise Roulin, Taoufik El Gnaoui, Fabrice Jardin, Nicolas Mounier, Hervé Tilly & Corinne Haioun (2021): Rituximab plus gemcitabine and oxaliplatin (R-GemOx) in refractory/relapsed diffuse large B-cell lymphoma: a real-life study in patients ineligible for autologous stem-cell transplantation, Leukemia & Lymphoma, DOI: 10.1080/10428194.2021.1901090

To link to this article: https://doi.org/10.1080/10428194.2021.1901090

Published online: 25 Mar 2021.

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2021.1901090

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Rituximab plus gemcitabine and oxaliplatin (R-GemOx) in refractory/relapsed diffuse large B-cell lymphoma: a real-life study in patients ineligible for autologous stem-cell transplantation

Clarisse Cazelles[a], Karim Belhadj[a], Hélène Vellemans[b], Vincent Camus[b], Elsa Poullot[c], Philippe Gaulard[c,d,e], Liana Veresezan[f], Emmanuel Itti[d,g], Stéphanie Becker[h], Muriel Carvalho[i], Jehan Dupuis[a], Fabien Le Bras[a], François Lemonnier[a,d,e], Louise Roulin[a], Taoufik El Gnaoui[a], Fabrice Jardin[b], Nicolas Mounier[j], Hervé Tilly[b] and Corinne Haioun[a,d,e]

[a]Lymphoid Malignancies Unit, Hôpital Henri Mondor, AP-HP, Créteil, France; [b]Department of Hematology and U1245, Rouen, France; [c]Department of Pathology, Hôpital Henri Mondor, AP-HP, Créteil, France; [d]Paris-East, Créteil University, Créteil, France; [e]INSERM U955, Mondor Biomedical Research Institute, Créteil, France; [f]Department of Pathology, Rouen, France; [g]Department of Nuclear Medicine, Hôpital Henri Mondor, AP-HP, Créteil, France; [h]Department of Nuclear Medicine, Rouen, France; [i]Department of Pharmacy, Hôpital Henri Mondor, AP-HP, Créteil, France; [j]Onco-Hematology Department, Hôpital l'Archet, Nice, France

ABSTRACT

There is no established standard treatment for relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) in patients who are not eligible to receive an intensive treatment. The combination of rituximab gemcitabine and oxaliplatin (R-GemOx) is widely used in this population but data are scarce. We retrospectively collected the data of 196 patients with R/R DLBCL treated with R-GemOx in two French centers over a period of 15 years. The median age of the population was 72 years (range, 24–89), 63% of the patients had an international prognostic index of 3 or higher and 57% were refractory to the last treatment. At the end of R-GemOx treatment, 33% of the patients obtained a complete response. The median progression-free survival (PFS) of the population was 5 months and the median overall survival (OS) was 10 months. Several factors were predictors of unfavorable survival: age over 75 years, international prognostic index of 2 or higher, refractory disease and de novo DLBCL. The median PFS and OS of the patients who obtained a complete response were 22 months and 40 months, respectively. The most significant toxicities were grade 3–4 hematological toxicities (31% of patients). Given its efficacy and tolerability, R-GemOx can be used in patients ineligible for intensive treatment and serve as a basis for new regimen combinations.

ARTICLE HISTORY
Received 23 October 2020
Revised 27 January 2021
Accepted 28 February 2021

KEYWORDS
Lymphoma and Hodgkin disease; prognostication; immunotherapy

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequently occurring subtype of non-Hodgkin's lymphoma, accounting for approximately 30 to 40% of new cases [1]. The incidence is especially high in patients aged 60 to 70 years [1,2]. The addition of rituximab to CHOP chemotherapy (R-CHOP) has improved the outcome of patients with DLBCL [3]. However, depending on their specific adverse prognostic factors, patients who relapse or are refractory to this frontline treatment, approximately 30 to 40% of the population, have a poor prognosis. Thus, improving the outcome of these patients represents an unmet medical need.

In relapsed or refractory (R/R) patients, the standard treatment consists of salvage immunochemotherapy followed by, for those who respond, intensive treatment with autologous stem cell transplantation (ASCT) [4,5]. However, a large proportion of R/R DLBCL patients are not eligible to receive this treatment due to age, comorbidities or because they have already received an ASCT [6]. A large number of combinations have been proposed in this patient population but none of them are recognized as a therapeutic standard [7]. The R-GemOX (rituximab, gemcitabine, and oxaliplatin) combination is one of the most widely used since the publication of a prospective study showing its efficacy and acceptable tolerability [8,9].

CONTACT Corinne Haioun corinne.haioun@aphp.fr Lymphoid Malignancies Unit, Hôpital Henri Mondor, 51 Avenue du Maréchal de Lattre de Tassigny, 94010, Créteil, France

However, since this publication, very few data have confirmed these results in patients with R/R DLBCL [10–12].

Here, we report the results of a large retrospective analysis of a cohort of R/R DLBCL patients not eligible for ASCT, all previously exposed to rituximab and doxorubicin, treated with R-GemOX in two academic centers in France. The main objective was to evaluate the efficacy and safety of this regimen in a large series of patients in a real-life setting.

Patients and methods

From May 2002 to May 2017, 196 patients with de novo or transformed R/R DLBCL were treated with R-GemOX at the Henri Mondor Hospital in Creteil or at the Henri Becquerel Center in Rouen, both academic university hospitals in France. All selected patients were previously treated with doxorubicin-based chemotherapy combined with rituximab and were considered to be ineligible for intensive treatment and ASCT by their treating physician, mainly because of age, comorbidities, or treatment failure after previous transplantation. Patients with a primary central nervous system lymphoma or immunosuppression-related lymphoma were excluded from this analysis. Refractory disease was defined as progressive or stable disease during previous treatment or relapse or progression within one year after the initiation of last treatment, regardless of the treatment line. Clinical characteristics (sex, age, Ann Arbor stage, performance status [PS], lactate dehydrogenase [LDH] level, and the International Prognostic Index [IPI] were collected at the time of the initiation of R-GemOx from the patient medical records. The study was conducted in accordance with the Declaration of Helsinki and with the approval of the Henri Becquerel Center Institutional Review Board (n°1905B).

Treatment, evaluation of response, and toxicity assessment

Treatment was administered as previously described[9]. Briefly, rituximab (375 mg/m^2) was delivered intravenously on day 1, and gemcitabine (1,000 mg/m^2) and oxaliplatin (100 mg/m^2) were administrated intravenously on day 2, every two weeks and continued for up to eight cycles if at least a PR was obtained after four cycles. No dose adjustment was planned in the event of hematological toxicity, but cycles were postponed until the absolute neutrophil count reached 1.0×10^9/L and the platelet count reached 100×10^9/L. The dose of oxaliplatin was adjusted in the event of peripheral neuropathy, as previously described[9]. Responses were evaluated after four cycles (induction phase) and at the end of treatment (after consolidation phase) by computed tomography (CT) or [18F] fluorodeoxyglucose positron emission tomography (PET), according to the availability of PET-CT.

Statistical analysis

The endpoints were overall response rate (ORR), complete response rate (CRR), PFS and OS. Responses were evaluated according to the International Workshop Group on Response Criteria [13]. Survival curves were estimated using the product-limit Kaplan–Meier method and compared using the log-rank test. All statistical analyses were performed using SEM software (Jean Perrin Center, France). The relative dose intensity (RDI), calculated per unit time, for gemcitabine and oxaliplatin was calculated according to the method of Hryniuk and Goodyear [14].

Results

Clinical characteristics

In total, 196 DLBCL patients were analyzed. The characteristics of the patients at initiation of R-GemOx are described in Table 1. The median age was 72 years (range, 24–89), and 123 (63%) patients had an IPI of 3 or higher. Thirty-two patients (16%) previously received an ASCT during the first-line treatment ($n = 4$) or after a previous relapse ($n = 28$). Eighty-eight patients (45%) had a history of indolent lymphoma, including simultaneous transformation at initial diagnosis for 31 patients. Previous indolent lymphoma consisted of follicular lymphoma in 57% of these patients. DLBCL subtypes were ascertained by immunohistochemistry based on the Hans algorithm [15] for 169 patients, with 77 patients (46%) identified to have the germinal center B-cell-like (GCB) subtype and 92 patients (54%) determine to have the non-germinal center B-cell like subtype. Three cases were classified as primary mediastinal B-cell lymphoma.

The median number of previous lines before R-GemOx was one (range 1–7). One hundred thirteen patients (58%) received R-GemOx as second line therapy, 45 (23%) as third line therapy, and 38 (19%) as fourth line therapy or more. One hundred and eleven patients were refractory to the last treatment before R-GemOx. The median time between initial diagnosis and the first cycle of R-GemOx was 13 months (range 2–134). Among patients treated in the second line

Table 1. Patient characteristics at initiation of R-GemOx.

	Patients (%)
Total	196 (100)
Sex (male)	107 (55)
Age groups, years	
• median (range)	72.0 (24–89)
• ≤65	34 (17)
• >65	162 (83)
Performance status:	
• 0–1	129 (66)
• 2 or more	66 (34)
• not available	1
Ann Arbor stage:	
• I–II	29 (15)
• III–IV	166 (85)
• not available	1
LDH:	
• within normal limits	83 (42)
• elevated	112 (57)
• not available	1
IPI risk groups :	
0	5 (3)
1	14 (7)
2	53 (27)
3	63 (32)
4	53 (27)
5	7 (4)
not available	1
Pathology:	
• DLBCL NOS	172 (88)
• Unclassifiable	20 (10)
• PMBL	3 (1)
• PTLD	1
Immunophenotype	169
Germinal center	77 (46)
Non germinal center	92 (54)
Previous history of indolent lymphoma	
No	108 (55)
Yes	88 (45)
Refractory disease to previous line	
Yes	82 (42)
No	111 (57)
Not known	3
Lines of prior anti-lymphoma therapies	
1	113 (58)
2 or more	83(42)
Previous ASCT	
Yes	32 (16)
No	164 (83)

LDH: lactate dehydrogenase; IPI: International Prognosis Index; NOS: not otherwise specified.

setting, the median duration between the initial diagnosis and the initiation of R-GemOx was 11 months (range 2–86).

Treatment delivery

As shown in Figure 1, 136 patients received at least four cycles and 61 patients completed the eight planned cycles. The disease progressed in 85 patients (43%) on therapy. Treatment was discontinued due to toxicity in 20 patients (10%). Upon the decision of their physicians, treatment was discontinued after six cycles in 13 CR patients.

The overall number of cycles administered was 979. The median number of cycles delivered per patient was five (range 1–8). Based on data collected from the

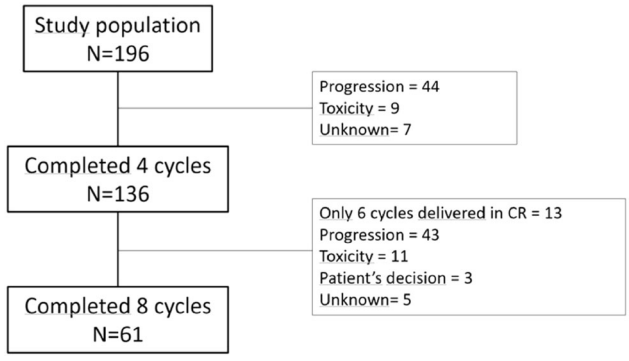

Figure 1. Patient disposition.

population that received the first four cycles (136 patients and 848 cycles), the median received dose intensities of oxaliplatin and gemcitabine were 73% and 76% of the theoretical dose, respectively. No dose intensity reduction was observed for rituximab.

Response to treatment and survival

After four cycles, 105 (54%) patients achieved a response and 45 (23%) achieved a CR. At the end of treatment, the ORR and CRR were 38% (75 patients) and 33% (64 patients), respectively (Table 2). The CRR was significantly higher for patients with a non-refractory status (50% vs 10%, $p < .001$). The CRR was also significantly higher for patients younger than 75 years (39% vs 23%, $p = .02$) and those with a low IPI (0–1: 47% vs 2–3: 39% vs 4–5 17%, $p = .005$). The CRR was similar when R-GemOx was delivered in the second line setting (32%) or in subsequent lines (34%).

With a median follow-up of 22 months, the median PFS and OS for the entire cohort were 5 and 10 months, respectively. The two-year PFS and two-year OS were 18% (95% CI: 13–25) and 32% (95% CI: 26–40), respectively (Figure 2). OS was significantly longer in patients who had a prior history of indolent lymphoma (median 21 vs 8 months, $p < .001$), non-refractory status (median 18 vs 7 months, $p < .001$), age younger than 75 years (median 16 vs 7 months, $p < .001$), or an IPI less than 3 (median 21 vs 8 months, $p < .001$) (Table 2, Figure 3). The number of previous lines of treatment (one or more) did not significantly affect PFS or OS. Having a GC or non-GC phenotype did not affect the outcome. The median PFS and OS of the 64 patients who achieved a CR were 22 months and 40 months respectively, their PFS and OS at 2 years being 50% (95% CI: 36–63) and 66% (95% CI: 53–77) respectively (Figure 3(D)).

Among patients who were treated with R-GemOx as second line therapy, the median PFS and OS were 4 and 10 months, respectively, which were not

Table 2. Response after completion of R-GemOx, progression free survival (PFS) and overall survival (OS) according to patient characteristics.

	N	CR (%)	*p*	PFS (median)	*p*	OS (median)	*p*
All patients	196	33		5		10	
Previous indolent lymphoma							
Yes	88	42	.57	6	<.001	21	<.001
No	108	26		3		8	
Refractory to previous therapy							
Yes	82	10	<.001	2	<.001	7	<.001
No	111	50		6		18	
Not available	3						
R-GemOx							
In 2nd line	113	32	.81	4	.75	10	.49
In 3rd line or more	83	34		5		12	
Age (years)							
<75	124	39	.02	6	.02	16	<.001
≥75	72	23		3		7	
International prognostic index							
0-1	19	47	.005	11	.007	27	<.001
2-3	116	38		5		15	
4-5	60	17		2		5	
Immunophenotype							
Germinal center	77	30	.86	4	.81	10	.52
Non germinal center	92	32		5		11	

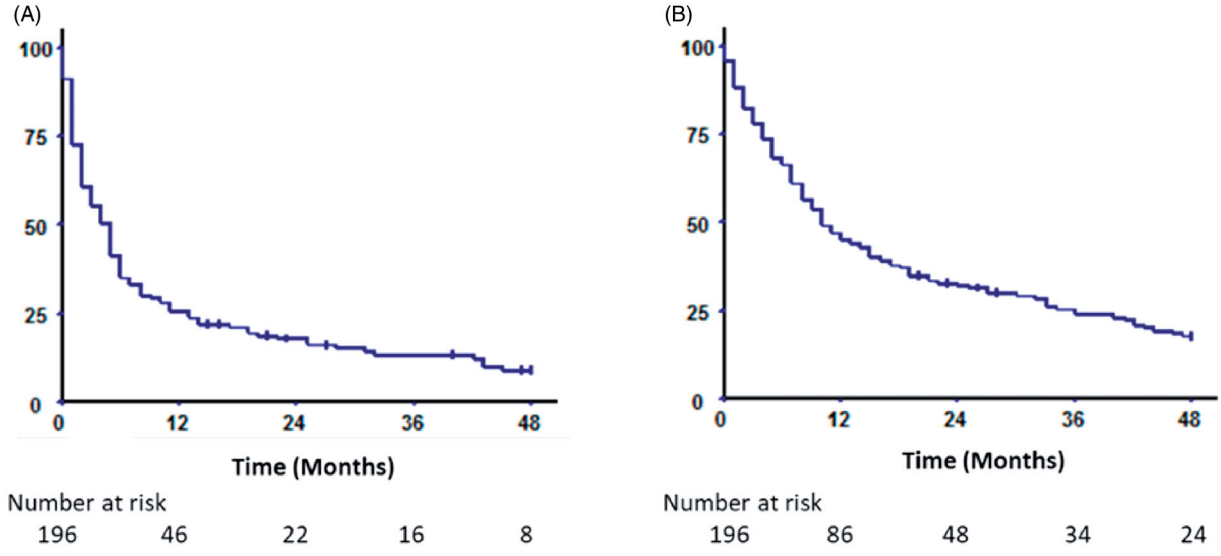

Figure 2. Outcome of the population. (A) PFS; median: 5 months. (B) OS; median: 10 months.

different from those values seen in patients who received R-GemOx in subsequent lines (Table 2). In this population, OS was also significantly longer in patients who had a non-refractory status, a response to first treatment longer than 12 months, a history of previous indolent lymphoma, an IPI less than 3 and age younger than 75 years.

Thirty-six patients have been previously treated (before R-GemOx) with platinum containing regimen, which count for 18% of the entire population. Ten out of these 36 (28%) patients achieved CR. This response rate is similar to the rate observed in the entire population. Thirty-two patients had previously received an ASCT. Thirteen of them (40%) achieved a CR with R-GEMOX. The median PFS and OS of these patients were 5 and 22 months, respectively.

Treatment toxicities

Grade 3–4 toxicities were observed for 31% of the patients and were mainly hematological. Thirty-five percent of patients required at least one red blood cell transfusion and 27% required at least one platelet transfusion during treatment. Sixty-eight hospitalizations or prolongations of hospitalization (7% of the 979 cycles) were observed during treatment, including

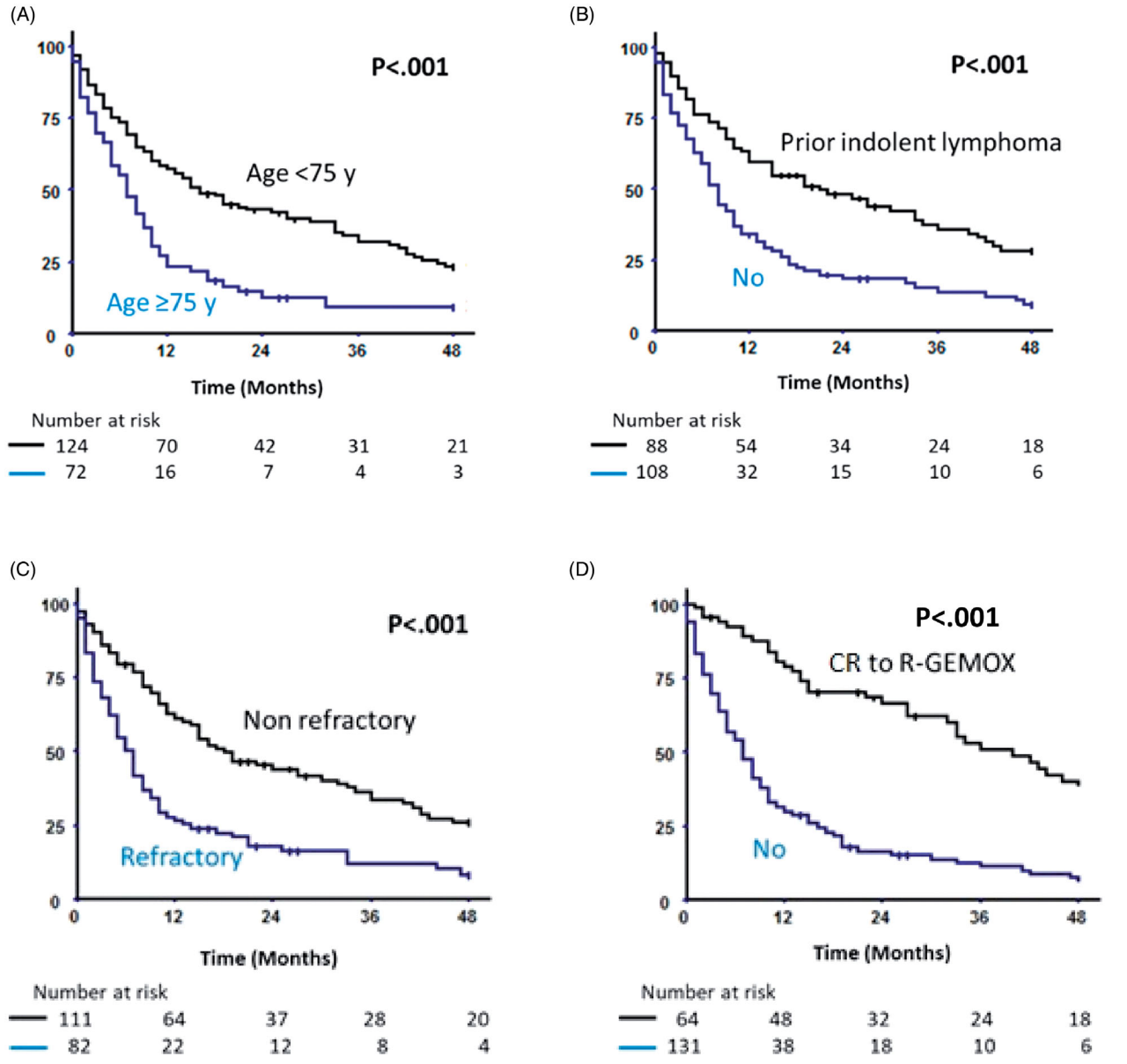

Figure 3. Overall survival according to select patient characteristics. (A) Age, <75 years; median: 16 months; mean: 75 years; median: 7 months. (B) Prior history of indolent disease, Yes; median: 21 months, No; median: 8 months. (C) Refractory to previous therapy, No; median: 7 months, Yes; median: 18 months. (D) Response to R-GemOx, Complete response; median: 40 months, Less than complete response; median: 7 months.

at least one hospitalization for febrile neutropenia for 22 patients, which was lethal for seven patients. Grade 1–2 peripheral sensory neuropathy was reported in 51 patients (26%) and grade 3 peripheral sensory neuropathy was reported in two patients. Neurotoxicity led to oxaliplatin discontinuation in 16 (8%) patients. No grade 3 or higher renal toxicity was observed.

Discussion

The R-GemOx regimen is a frequently used treatment for R/R DLBCL and is listed in the NCCN and ESMO guidelines based on results from phase II clinical trials [16]. However, there is a paucity of observational data in a real-life setting showing the efficacy of R-GemOx.

We conducted a retrospective analysis of the use of this regimen in 196 patients with R/R DLBCL treated at two university hospitals over a period of 15 years. Our primary objective was to evaluate the activity of this regimen as measured by response and outcome. Given the limitations of retrospective studies, it was difficult to collect accurate data on toxicities. R-GemOx is usually offered to patients who are not eligible for intensive treatment and transplantation. This explains the median age of 72 years for this cohort.

With a CR rate of 33%, a median PFS of 5 months and a median OS of 10 months, the results of this retrospective study are very close to those described in the only published prospective phase 2 study in 49 patients in a similar population of R/R DLBCL patients. The usual adverse prognostic factors for R/R DLBCL were found in this cohort: older age of patients, refractory nature of the disease, short first remission duration and advanced stage. On the other hand, the number of previous lines of treatment and the phenotypically defined cell of origin did not seem to influence the clinical course. As has already been shown, patients with a complete response to R-GemOx can achieve a long-term survival.

As previously described [9], the most predominant side effect was hematological toxicity, which was responsible for febrile neutropenia episodes and hospitalizations. Peripheral sensory neuropathy, considered to be related to oxaliplatin treatment, occurred in 26% of the patients but was, in the vast majority of cases, of mild intensity and reversible. The lack of severe renal toxicity observed here confirms previous observations and is particularly advantageous when treatment is considered in heavily pretreated patients or elderly patients with comorbidities.

There is no established standard treatment for R/R DLBCL patients who are not eligible for ASCT. The results observed with R-GemOx compare favorably with those of other combinations of rituximab and chemotherapy in the R/R setting for patients previously exposed to rituximab such as rituximab-ifosfamide-etoposide [17], rituximab-bendamustine [18], or rituximab-vinorelbine-ifosfamide-mitoxantrone-prednisone [19] regimens, mainly because of the better tolerability of R-GemOx.

The combination of lenalidomide and rituximab (R2 regimen) has demonstrated promising efficacy in R/R DLBCL [20]. A combination of obinutuzumab and lenalidomide was considered to be more efficient than the R2 regimen, while showing a good safety profile [21]. However, the outcome in a phase II study of this regimen, in a population of R/R DLBCL patients was unsatisfactory, with an ORR at the end of induction treatment of 35% and a median PFS of 4.1 months, suggesting that it is not superior to the R2 regimen [22].

More recently, a randomized phase 2 trial studied the combination of polatuzumab vedotin (PV) in combination with bendamustine and rituximab (BR) compared with BR in patients ineligible for ASCT [23]. In this trial, the PV-BR combination had a higher CR rate, a longer PFS and OS than the BR regimen. All subgroups examined appeared to benefit from the combination, including refractory patients and those who received multiple prior lines of therapy. The trial design and modest sample size were potential limitations of the study but following these results the FDA and EMA approved PV in combination with BR in R/R DLBCL.

CAR T cells therapy has become an important option for patients with R/R DLBCL, and today, many of the patients in this cohort would have been treated this way. It is interesting to compare the outcome of patients who achieved a complete response with R-GemOx and those who received treatment with axicabtagene ciloleucel [24,25]. Furthermore, the properties of R-GemOx could make it a good candidate in cases where a bridging therapy for CAR T cells is needed.

Due to its wide use in the clinic, R-GemOx is currently being used as a comparator arm in two ongoing phase 3 in populations of R/R DLBCL patients who are not eligible for ASCT. These two studies are investigating the potential benefit of combining a targeted drug with R-GemOx. The NIVEAU trial (NCT03366272) is evaluating the use of the human anti-PD1 antibody nivolumab, which has the potential to increase rituximab-mediated effector mechanism and target the microenvironment. The POLARGO trial (NCT03274492) is studying PV in combination with R-GemOx, in the same setting. Moreover, GemOx is also being evaluated in combination with two CD20-CD3 bispecific antibodies, glofitamab or mosunetuzumab, in a Phase Ib trial in R/R DLBCL (NCT04313608).

Furthermore, R-GemOx has been studied as a front-line treatment for elderly patients with DLBCL [26]. In this setting, the efficacy and safety of the combination encouraged the initiation of a phase 3 trial comparing R-GemOx and the standard R-miniCHOP in patients older than 80 years (NCT02767674).

This study provides real life data related to R-GemOx efficacy and safety in a sizable cohort of R/R DLBCL patients ineligible for transplant. It could improve sample size calculation for upcoming trials, and could provide a useful comparison with real life series of patients treated with more recent therapeutics, such as CAR-T cells.

Author contributions

Corinne Haioun and Hervé Tilly designed the study. Clarisse Cazelles, Karim Belhadj, Corinne Haioun and Hervé Tilly wrote the manuscript. Clarisse Cazelles and Hélène Vellemans collected the data. Elsa Poullot, Philippe Gaulard and Liana Veresezan reviewed the pathology samples.

Emmanuel Itti and, Stéphanie Becker reviewed PET-CT data. Vincent Camus, Muriel Carvalho, Jehan Dupuis, Fabien Le Bras, François Lemonnier, Louise Roulin, Taoufik El Gnaoui, and Fabrice Jardin provided data. Hervé Tilly, Corinne Haioun and Nicolas Mounier analyzed and interpreted data. All authors reviewed the manuscript and approved the final version.

Disclosure statement

Karim Belhadj received honoraria from Celgene, Leo pharma, Amgen, Sanofi, Janssen-Cilag, Takeda. Vincent Camus received honoraria from Roche. Philippe Gaulard received research fundings from Innate Pharma, Takeda, and Sanofi and honoraria from Takeda and Gilead. Francois Lemonnier received honoraria from Miltenyi, and grant travel from Celgene and Janssen. Fabrice Jardin received honoraria from Roche. Hervé Tilly received honoraria from Roche, Karyopharm, Astra-Zeneca, Janssen-Cilag and Servier. Corinne Haioun received honoraria from Roche, Janssen-Cilag, Gilead, Takeda, Miltenyi and Servier and travel grants from Amgen and Celgene. The other authors have no conflict of interest to declare.

References

[1] Medical history, lifestyle, family history, and occupational risk factors for diffuse large B-cell lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project - NCBI. [cited 2020 Mar 3]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/?cmd=HistorySearch&querykey=1.

[2] Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin. 2016;66(6):443–459.

[3] Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346(4):235–242.

[4] Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995;333(23):1540–1545.

[5] Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(27):4184–4190.

[6] Coiffier B, Thieblemont C, Van Den Neste E, et al. 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. Blood. 2010;116(12):2040–2045.

[7] Salles GA, Pettengell R, Cordoba R, et al. Treatment of aggressive B-cell non-Hodgkin lymphoma beyond frontline therapy in patients not eligible for stem cell transplantation: a structured review. Leuk Lymphoma. 2019;60(7):1610–1625.

[8] El Gnaoui T, Dupuis J, Belhadj K, et al. Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. Ann Oncol. 2007;18(8):1363–1368.

[9] Mounier N, El Gnaoui T, Tilly H, et al. 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. Haematologica. 2013;98(11):1726–1731.

[10] Corazzelli G, Capobianco G, Arcamone M, et al. Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma. Cancer Chemother Pharmacol. 2009;64(5):907–916.

[11] Dhanapal V, Gunasekara M, Lianwea C, et al. Outcome for patients with relapsed/refractory aggressive lymphoma treated with gemcitabine and oxaliplatin with or without rituximab; a retrospective, multicentre study. Leuk Lymphoma. 2017;58:1–9.

[12] Cabanillas F, Rivera N, Acosta M, et al. A new salvage regimen for aggressive lymphomas based on gemcitabine, rituximab, and oxaliplatin followed by lenalidomide (GROC-Rev). Clin Lymphoma Myeloma Leuk. 2019;19(12):776–783.

[13] Cheson BD, Pfistner B, Juweid ME, International Harmonization Project on Lymphoma, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579–586.

[14] Hryniuk WM, Goodyear M. The calculation of received dose intensity. J Clin Oncol. 1990;8(12):1935–1937.

[15] Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood. 2004;103(1):275–282.

[16] Tilly H, Gomes da Silva M, Vitolo U, ESMO Guidelines Committee, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v116–125.

[17] Joshi M, Taper J, Forsyth C, et al. Outpatient rituximab, ifosfamide, etoposide (R-IE) in patients older than 60 years with relapsed or refractory diffuse large B-cell lymphoma who are not candidates for stem cell transplantation. Leuk Lymphoma. 2020;61(1):91–97.

[18] Ohmachi K, Niitsu N, Uchida T, et al. Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol. 2013;31(17):2103–2109.

[19] Gyan E, Damotte D, Courby S, GOELAMS Group, et al. High response rate and acceptable toxicity of a combination of rituximab, vinorelbine, ifosfamide, mitoxantrone and prednisone for the treatment of diffuse large B-cell lymphoma in first relapse: results of the R-NIMP GOELAMS study. Br J Haematol. 2013;162(2):240–249.

[20] Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma:

a phase II clinical trial. Leukemia. 2013;27(9): 1902–1909.
[21] Morschhauser F, Salles G, Le Gouill S, et al. An open-label phase 1b study of obinutuzumab plus lenalidomide in relapsed/refractory follicular B-cell lymphoma. Blood. 2018;132(14):1486–1494.
[22] Houot R, Cartron G, Bijou F, et al. Obinutuzumab plus Lenalidomide (GALEN) for the treatment of relapse/refractory aggressive lymphoma: a phase II LYSA study. Leukemia. 2019;33(3):776–780.
[23] Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol. 2020;38(2):155–165.
[24] Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019;20(1):31–42.
[25] Jacobson CA, Hunter BD, Redd R, et al. Axicabtagene ciloleucel in the non-trial setting: outcomes and correlates of response, resistance, and toxicity. J Clin Oncol. 2020;38(27):3095–3106.
[26] Shen Q-D, Zhu H-Y, Wang L, et al. Gemcitabine-oxaliplatin plus rituximab (R-GemOx) as first-line treatment in elderly patients with diffuse large B-cell lymphoma: a single-arm, open-label, phase 2 trial. Lancet Haematol. 2018;5(6):e261–e269.