EFFICACY AND SAFETY OF R-GEMOX IN RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA: A SINGLE-CENTER EXPERIENCE IN VIETNAM

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Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL), yet a substantial proportion of patients experience relapse or refractory disease following initial therapy. Among various salvage regimens, R-GEMOX - comprising rituximab, gemcitabine, and oxaliplatin - has shown promising efficacy and a tolerable safety profile. This retrospective cohort study aimed to evaluate the treatment outcomes and adverse events associated with R-GEMOX in patients with relapsed or refractory CD20-positive DLBCL treated at Hanoi Oncology Hospital. A total of 39 patients who received at least four cycles of R-GEMOX between January 2018 and May 2024 were included. Treatment response was assessed using the Lugano 2014 criteria, and toxicities were graded per CTCAE v4.0. The median age of the cohort was 57.2 years old. The overall response rate (ORR) was 69.2%, including a complete response rate of 28.2% and a partial response rate of 41.0%. Stable disease and progressive disease were observed in 7.7% and 23.1% of patients, respectively. Grade 3-4 hematologic toxicities occurred in 30.8% of cases. Median progression-free survival (PFS) was 9.5 months, while median overall survival (OS) reached 15.7 months. These findings suggest that R-GEMOX is an effective and tolerable salvage regimen in the management of relapsed/refractory DLBCL, particularly for patients ineligible for high-dose chemotherapy or stem cell transplantation.

Keywords: DLBCL, non-Hodgkin lymphoma, R-GEMOX, salvage chemotherapy, relapsed/refractory, Vietnam.

I. INTRODUCTION

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of malignant lymphoproliferative disorders. In Vietnam, the ASIR (Age Standardized Incidence Rate) is 3.5 per 100,000 in males and 3.0 per 100,000 in females, with an average of 3.2 per 100,000 for both sexes, making NHL one of the 13 most prevalent malignancies in the country.[1] NHL is among the hematologic malignancies with potential for cure. Advances in chemotherapy, radiotherapy, and monoclonal antibody therapies have contributed to long-term remission in a subset of patients, with 5-year survival rates ranging from 30% to 55%.[2] Nonetheless, a considerable proportion of patients experience disease relapse or exhibit resistance to frontline treatment. Among the histological subtypes of NHL, diffuse large B-cell lymphoma (DLBCL) constitutes the most common and aggressive form, characterized by rapid progression and a high rate of recurrence.[3] Approximately 50 - 60% of patients with DLBCL achieve and maintain complete remission following first-line treatment; however, 30 - 40% eventually relapse, and 10% are refractory to initial therapy.[4,5] Treating relapsed or refractory

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(R/R) NHL remains challenging, particularly as patients often present with reduced performance status due to prior intensive chemotherapy regimens.

Globally, various salvage chemotherapy protocols have been employed in R/R NHL with the goal of achieving remission prior to high-dose chemotherapy and autologous stem cell transplantation (ASCT), which may prolong survival. However, not all patients are suitable candidates for this approach due to comorbidities, poor clinical status, or limited access. This is particularly relevant in Vietnam, where access to ASCT and novel therapies such as CAR-T remains limited. For such patients, salvage chemotherapy remains the primary treatment strategy. Regimens such as R-ICE, R-GDP, R-DHAP, R-ESHAP, and R-GEMOX have demonstrated efficacy in extending both progression-free survival (PFS) and overall survival (OS) in this patient population.[6-9] The R-GEMOX regimen, consisting of rituximab, gemcitabine, and oxaliplatin, has been introduced as a salvage option for patients with R/R NHL. Multiple studies have highlighted its favorable efficacy and tolerability profile.[10,11] In recent years, this regimen has been applied in clinical practice at Hanoi Oncology Hospital; however, no study has yet been conducted to assess its therapeutic outcomes and toxicity. This study was therefore designed to evaluate the effectiveness and safety of the R-GEMOX regimen in patients with relapsed or refractory DLBCL.

II. MATERIALS AND METHODS

1. Subjects

Enrolling patients ≥ 18 years with CD20+ DLBCL who experienced relapsed or were refractory after receiving first-line treatment. Eligible patients had ECOG 0-2, received ≥ 4 cycles of R-GEMOX, with no prior gemcitabine, HDCT, or ASCT. Inclusion required adequate organ function (unless cytopenia due to marrow infiltration) and complete medical records. Exclusion criteria included active systemic infections, CNS involvement at diagnosis, or life-threatening comorbidities.

2. Methods

Study design

A retrospective cohort study was conducted at Hanoi Oncology Hospital (01/2018 - 05/2024).

Sample size

The sample size was based on a 12-month OS rate of 30%, with a 95% confidence level and 15% margin of error. After adjusting for a potential 10% loss to follow-up, 39 patients were recruited.

Treatment schedule and assessments

All eligible patients received R-GEMOX every 14 days, consisting of rituximab 375 mg/m² (day 1), gemcitabine 1000 mg/m² (day 1), and oxaliplatin 100 mg/m² (day 1), administered intravenously. The treatment course ranged from 4 to 8 cycles based on response and tolerability. Supportive care, including hydration, antiemetics, and dose adjustments for toxicity, was provided as if clinically indicated.

Baseline and follow-up evaluations included physical examination, blood tests, and imaging at diagnosis, before each cycle, and after 4 and 8 cycles of treatment. Treatment response was assessed per Lugano 2014 criteria, and adverse events were graded using CTCAE v4.0.

Study outcomes

The primary endpoints of the study were progression-free survival (PFS) and overall survival (OS). PFS was measured as the time from initiation of R-GEMOX therapy to either documented disease progression or death from any cause, whichever occurred first. OS was defined as the time from treatment initiation

to death from any causeor the last recorded follow-up. Survival durations were calculated in months by dividing the number of days between key events by 30.45. Patients who remained alive and progression-free at the time of analysis were censored at their last known date of contact.

Secondary endpoints included radiologic treatment response according to the Lugano 2014 criteria and the incidence of grade 3-4 treatment-related toxicities. Tumor response was assessed by imaging after 4 and 8 cycles of R-GEMOX. Per Lugano 2014 definitions, responses were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), with CR and PR collectively defined as objective responses.[12]

Adverse events were monitored throughout the treatment period and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Hematologic toxicities included anemia, neutropenia, and thrombocytopenia, while non-hematologic events encompassed gastrointestinal symptoms, peripheral neuropathy, and elevations in serum transaminases or creatinine. All chemotherapy delays, dose reductions, or treatment interruptions due to toxicity were documented.

Statistical analysis

All data were coded and analyzed using SPSS version 20.0. Descriptive statistics were used to summarize baseline characteristics, treatment response, toxicity, and survival outcomes. Categorical variables were compared using Fisher's exact test. Kaplan–Meier analysis was performed to estimate PFS and OS, and differences in survival were assessed using the log-rank test. Multivariate logistic regression was conducted to identify factors associated with treatment response. A p-value less than 0.05 was considered statistically significant.

3. Research ethics

The study was approved by the Ethics Board of Hanoi Oncology Hospital (No. 3220/QD-BVUB, 29/10/2024). All procedures followed routine care, and data were anonymized and handled confidentially.

III. RESULTS

1. Patient characteristics

A total of 39 patients with relapsed or refractory DLBCL were enrolled. The mean age was 57.2 ± 12.6 years old (range 29 - 77), and 53.8% were female. Most patients had an ECOG performance status at time of treatment initiation of 0 (61.5%) and presented with peripheral lymphadenopathy (79.4%). Approximately 30.8% of patients were classified as primary refractory. The majority had received one prior line of chemotherapy (84.6%), and the median interval from the last treatment to R-GEMOX initiation was 14.5 months (range 3 - 52). Stage III disease accounted for 54% of the cohort. Histologically, 59% of patients had the non-germinal center subtype, and 17.9% had evidence of histologic transformation. Most patients had received only one prior regimen before R-GEMOX (84.6%) (Table 1).

2. Treatment response

Patients received a median of 6.2 cycles of R-GEMOX (range 3 - 8). At interim evaluation (after 4 cycles), the overall response rate (ORR) was 74.4%, including 10.3% complete responses. At end-of-treatment, the ORR was 66.7%, with 12.8% complete responses and 53.9% partial responses. The progressive disease rate rose from 17.9% to 33.3% from mid- to end-of-treatment (Table 2).

Table 1. Baseline characteristics of the study population (n = 39)

Characteristic	Results
Age, mean ± SD (range)	57.2 ± 12.6 (29 - 77)
Gender, n (%)	
Male	18 (46.2)
Female	21 (53.8)
ECOG performance status at time of treatment initiation, n (%)	
0	24 (61.5)
1	11 (28.2)
2	4 (10.3)
B symptoms, n (%)	4 (10.3)
Primary refractory disease, n (%)	12 (30.8)
Median interval since last regimen (mo)	14.5 (3 - 52)
Stage III disease, n (%)	21 (54.0)
Non-GCB subtype, n (%)	23 (59.0)
Histologic transformation, n (%)	7 (17.9)
Number of prior regimens, n (%)	
1 regimen	33 (84.6)
≥ 2 regimens	6 (15.4)

Table 2. Treatment response to R-GEMOX (n = 39)

Response category	Interim, n (%)	End of treatment, n (%)
Complete response (CR)	4 (10.3)	5 (12.8)
Partial response (PR)	25 (64.1)	21 (53.9)
Stable disease (SD)	3 (7.7)	0
Progressive disease (PD)	7 (17.9)	13 (33.3)
Overall response (CR + PR)	29 (74.4)	26 (66.7)

3. Toxicity profile

Grade ≥ 3 adverse events were recorded in 20.5% of patients. The most frequent toxicities included fatigue (64.1%), anemia (33.3%), thrombocytopenia (25.6%), and gastrointestinal symptoms (25.6%). Grade 3-4 neutropenia occurred in 12.8% of patients, with one case of febrile neutropenia. No treatment-related renal toxicity was observed (Table 3).

Table 3. Treatment-related toxicities (n = 39)

Category	Adverse Event	Results
Clinical toxicities	Fatigue	25 (64.1)
	Nausea/vomiting	10 (25.6)
	Peripheral neuropathy	4 (10.3)
Hematologic toxicities	Anemia	13 (33.3)
	Thrombocytopenia	10 (25.6)
	Grade 3-4 neutropenia	5 (12.8)
	Febrile neutropenia	1 (2.6)
Liver/renal toxicities	Elevated liver enzymes	10 (25.6)
	Renal toxicity	0
Overall severe toxicity	Grade ≥ 3 toxicity (any)	8 (20.5)

4. Survival outcomes

The median progression-free survival (PFS) was 14.0 months, and the median overall survival (OS) was 21.1 months. At 12 months, PFS and OS rates were 50.7% and 82.9%, respectively. At 24 months, PFS and OS were 33.8% and 65.7%, respectively. Kaplan-Meier survival curves are presented in Chart 1.

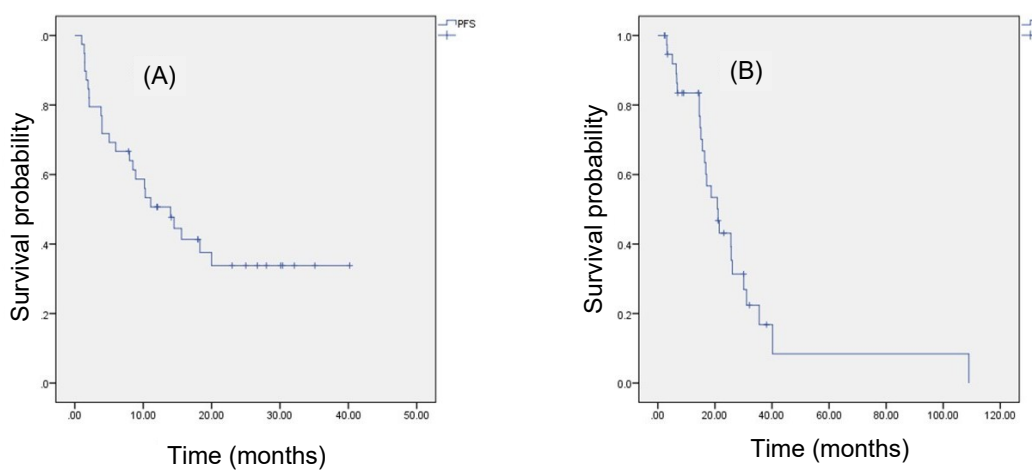

Chart 1. Kaplan–Meier survival curves: (A) Progression-free survival; (B) Overall survival

Refractory disease and histologic transformation were associated with worse outcomes in terms of both OS and PFS. Advanced-stage disease showed a trend toward poorer prognosis, while age and prior treatment lines were not significant predictors in this model.

Table 4. Multivariate Cox regression for factors associated with overall survival (OS) and progression-free survival (PFS)

Variable	HR for OS (95% CI)	HR for PFS (95% CI)
Refractory disease (yes vs. no)	2.41 (1.01 - 5.76)	2.65 (1.14 - 6.14)
Stage III-IV (vs. I-II)	1.89 (0.85 - 4.18)	2.08 (0.94 - 4.61)
Histologic transformation (yes vs. no)	2.75 (1.12 - 6.71)	2.39 (1.03 - 5.52)
Number of prior regimens (≥ 2 vs. 1)	1.48 (0.61 - 3.58)	1.36 (0.56 - 3.28)
Age ≥ 60 (vs. < 60)	1.21 (0.53 - 2.76)	1.17 (0.49 - 2.79)

I. DISCUSSION

In patients with relapsed or refractory diffuse large B-cell lymphoma, therapeutic options are often limited, especially in settings where high-dose chemotherapy and autologous stem cell transplantation (ASCT) remain inaccessible or contraindicated. While ASCT is considered standard for fit patients responding to salvage chemotherapy, a substantial proportion of patients are not candidates due to comorbidities, poor performance status, or logistical limitations. In these cases, palliative chemotherapy remains the mainstay to prolong survival and improve disease control. Our study focused on such a population-patients ineligible for ASCT-receiving R-GEMOX as second-line treatment. The observed median progression-free survival (PFS) was 14.0 months, and overall survival (OS) was 21.1 months, with 2-year PFS and OS rates of 33.8% and 65.7%, respectively. These results are comparable to previous findings. Gnaoui et al. reported a 2-year OS of 66% and PFS of 43% with R-GEMOX in a similar setting, while Cazelles et al. noted shorter median PFS and OS of 5 and 10 months, respectively, potentially due to more heavily pretreated populations.[10,11]

The R-GEMOX regimen demonstrated promising activity in this cohort, with an overall response rate (ORR) of 74.4% at interim and 66.7% at end-of-treatment. These rates are comparable or superior to other salvage regimens used in similar populations. Gnaoui reported an ORR of 83% (CR 50%), Cazelles observed end-of-treatment ORR of 38% (CR 33%), while Hou reported an ORR of 72% (CR 56%) after 2 cycles.[10,11,13] The difference in response rates between our study and others may reflect differences in treatment sequencing. Most patients in our cohort received R-GEMOX as second-line therapy, whereas in previous studies, many had undergone multiple prior regimens before receiving R-GEMOX, which may have contributed to a lower overall response rate.

Our multivariate Cox regression identified refractory disease and histologic transformation as independent predictors of inferior OS and PFS. These findings align with those of Yun Hou et al., who demonstrated significantly lower 2-year OS and PFS in refractory patients (50% and 38%) compared to relapsed ones (85% and 66%).[13] These data underscore the biological aggressiveness and chemoresistance of refractory DLBCL, reinforcing the need for novel approaches such as CAR-T cell therapy or early access to transplant when feasible. Despite international advances in second-line management - including the PARMA

trial's validation of ASCT in chemosensitive relapsed DLBCL and recent phase III trials (TRANSFORM, ZUMA-7) confirming the superiority of CD19-directed CAR-T therapy over conventional salvage/ASCT in high-risk patients - such modalities remain largely inaccessible in Vietnam.[14,15] This highlights the practical value of accessible regimens like R-GEMOX for disease control in real-world, resource-constrained settings.

Regarding safety, R-GEMOX was generally well tolerated. Grade ≥ 3 adverse events occurred in 20.5% of patients, with hematologic toxicity being the most common, particularly anemia (33.3%), thrombocytopenia (25.6%), and neutropenia (12.8%). No treatment-related mortality was observed. These findings compare favorably with other reports: El Gnaoui et al. reported grade 3-4 neutropenia and thrombocytopenia in 44% and 23% of patients, respectively, with 19.6% requiring platelet transfusion, while Cazelles et al. also reported frequent transfusion needs and febrile neutropenia in 2.2% of cycles.[10,11] The relatively lower toxicity rates in our study may be attributed to multiple factors, including the prophylactic use of G-CSF, better bone marrow reserve due to fewer prior lines of therapy, and absence of prior transplant exposure. These findings suggest that R-GEMOX is a feasible and acceptable option for patients unable to pursue more intensive strategies.

V. CONCLUSION

The R-GEMOX regimen appears to be an effective and well-tolerated salvage option for patients with relapsed or refractory DLBCL who are ineligible for autologous stem cell transplantation. Its real-world applicability is particularly relevant in resource-limited settings. Poorer outcomes in refractory and transformed cases highlight the need for early risk stratification and tailored treatment approaches. Future studies should explore biomarkers, optimize patient selection, and compare R-GEMOX with other salvage regimens in prospective settings.

DECLARATIONS

Conflicting interests

The authors declare no competing interests in preparing this article.

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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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