Am J Cancer Res 2025;15(12):5364-5373
www.ajcr.us /ISSN:2156-6976/ajcr0168608

Original Article

Selinexor combined with R-GDP as salvage therapy in relapsed/refractory diffuse large B-cell lymphoma

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Received September 6, 2025; Accepted December 25, 2025; Epub December 25, 2025; Published December 30, 2025

Abstract: Relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) remains a therapeutic challenge with poor prognosis. Selinexor, a selective inhibitor of nuclear export (XPO1), has shown activity in this setting. We retrospectively evaluated the efficacy and safety of selinexor combined with R-GDP (rituximab, gemcitabine, dexamethasone, and cisplatin) as second-line therapy in 22 patients with R/R DLBCL treated at Fudan University Shanghai Cancer Center between January 2023 and August 2023. Patients were scheduled to receive 3 cycles of selinexor plus R-GDP, and subsequently followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT), anti-CD19 chimeric antigen receptor T-cell (CAR-T) therapy, or alternative regimens, as appropriate. At a median follow-up of 25.5 months, the selinexor plus R-GDP regimen yielded an overall response rate of 52.4% in patients with R/R DLBCL. The median overall survival (OS) was 26.9 months (95% CI, 12.1-not reached), with 1- and 2-year OS rates of 67.6% and 52.3%. The median progression-free survival (PFS) was 7.7 months (95% CI, 2.27-not reached). Survival outcomes were significantly influenced by subsequent therapy: patients bridged to ASCT or CAR-T therapy had significantly longer OS (P=0.0217) and PFS (P=0.0029) than those receiving other treatments. The median OS was not reached in the ASCT group, 26.9 months (95% CI, 15.9-not reached) in the CAR-T group, and 11.2 months (95% CI, 10.2-not reached) in patients receiving other therapies. The median PFS was not reached for ASCT or CAR-T group, compared with 2.2 months (95% CI, 2.1-not reached) in patients receiving other therapies. Additionally, patients with relapsed disease exhibited a significantly longer median PFS than those with primary refractory disease (not reached vs 2.82 months, [95% CI, 2.17-not reached]; P=0.0072). No significant difference in OS was observed between these two groups (P=0.2323). Common adverse events included thrombocytopenia (100%), fatigue (59%), neutropenia (45%), anemia (45%), and pneumonia (23%), while were manageable through supportive care or temporary dose interruption. In this real-world analysis, selinexor combined with R-GDP demonstrated modest efficacy in R/R DLBCL, while highlighting the importance of optimizing subsequent sequencing with ASCT or CAR-T therapy.

Keywords: Selinexor, R-GDP, relapsed/refractory, diffuse large B-cell lymphoma (DLBCL), ASCT, CAR-T

Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma [1]. Most patients achieve remission with frontline rituximab-based immunochemotherapy; however, approximately 10-15% present with primary refractory disease, and 20-25% relapse after an initial response [2]. Outcomes remain poor for refractory patients, with a median overall survival (OS) of only 6.3 months reported in the SCHOLAR-1 study [3]. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) has long been the standard of care for transplant-eligible patients with relapsed or refractory DLBCL (R/R DLBCL), offering a potential second chance for cure [4]. Nevertheless, due to clinical constraints and variable responses to salvage therapy, only 25-35% of R/R DLBCL patients ultimately achieve long-term remission [2]. Platinum-based regimens such as rituximab with dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP), rituximab with ifosfamide, carboplatin, and etoposide (R-ICE), and rituximab with gemcitabine, dexamethasone, and cisplat-

https://doi.org/10.62347/RKWU3795

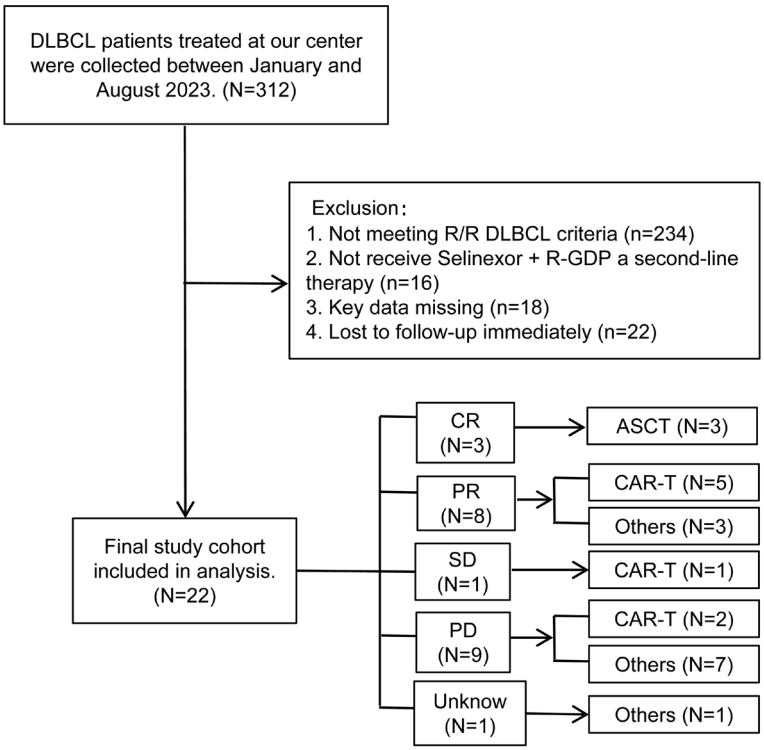

Figure 1. Flow diagram of patient screening, inclusion, treatment, and follow-up. This diagram illustrates the sequential process of identifying the final study cohort from the institutional EMR database. The initial query, sequential application of eligibility criteria, and resulting exclusions are shown. The final cohort (n=22) consisted of patients with sufficient and verifiable data for analysis. EMR: Electronic medical record; R/R DLBCL: Relapsed/refractory diffuse large B-cell lymphoma; ASCT: Autologous stem cell transplantation; CAR-T: Chimeric antigen receptor T-cell; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

in (R-GDP) remain the most commonly used salvage therapies, but their efficacy is modest, with overall response rates (ORR) of approximately 50% [5, 6]. Thus, novel salvage approaches are urgently needed to improve outcomes and enable more patients to proceed to ASCT.

Selinexor, an oral selective inhibitor of nuclear export (SINE), leading to the accumulation of tumor suppressor proteins in the nucleus and subsequent inhibition of tumor cell growth, has emerged as a novel therapeutic agent in a few hematological cancers [7, 8]. Based on the results of an international multicenter phase 2 trial (SADAL) [9], Food and Drug Administration (FDA) has granted approval of single-agent selinexor to patients with R/R DLBCL who had received at least two prior lines of systemic therapy. Combination studies involving selinexor and other agents targeting DLBCL have yielded promising preliminary results. The overall response rate (ORR) was 67%, and the median duration of response (DOR) was not reached among 18 patients with R/R B-cell lymphoma treated with selinexor in combination with R-GDP, and the recommended phase 2 dose of selinexor for this regimen was 40 mg per week [10]. Selinexor in combination with rituximab-lenalidomide (R2) demonstrated an ORR of 66.7% and a median progression-free survival (PFS) of 11.2 months among 12 patients with R/R DLBCL who were ineligible for ASCT [11].

Given these promising early findings and the unmet need for more effective salvage therapies before ASCT, we conducted a retrospective study to evaluate the efficacy and safety of selinexor combined with R-GDP/GDP as second-line salvage therapy in a real-world cohort of patients with R/R DLBCL.

Materials and methods

Patients

We included all consecutively treated patients with pathologically confirmed R/R DLBCL who received selinexor in combination with R-GDP/GDP at Fudan University Shanghai Cancer Center between January 2023 and August 2023. Medical records of eligible patients were reviewed to extract clinicopathologic features, disease histories, and outcomes. The process of patient screening, inclusion, treatment, and follow-up from the electronic medical record is summarized in a flow diagram (**Figure 1**) in the Results section. Double-expression DLBCL is defined as DLBCL patients exhibiting a C-MYC protein expression rate exceeding 40% and a BCL-2 protein expression rate exceeding 50% in immunohistochemical analysis. Data were

registered using Research Electronic Data capture software (REDcap; https://projectredcap.org/), thus guaranteeing the confidentiality of the information. This retrospective study was approved by the institutional ethics committee of the Institutional Review Board of Fudan University Shanghai Cancer Center (No. 2511-Exp316) and was in accordance with the Declaration of Helsinki ensuring patient safety and scientific rationale. Written informed consent was obtained from all participants for the treatment and for their data to be used for research purposes, clearly stating the experimental nature of the treatment.

Treatment and assessment

Patients received selinexor in conjunction with the R-GDP regimen, as determined by the treating physician's clinical discretion. Selinexor was administered orally (40 mg on day 1, 8, 15) plus R-GDP (R 375 mg/m^2 on day 1, gemcitabine 1 g/m^2 on day 1, cisplatin 25 mg/m^2 on days 1-3, dexamethasone 40 mg on days 1-4) every 3 weeks. Notably, one patient received selinexor in combination with GDP. This patient with DLBCL invaded the small intestine presented with a significant tumor burden and abdominal pain prior to treatment. Given the potential risk of perforation due to rapid tumor regression following rituximab administration according to previous relevant reports [12, 13], the decision was made to use GDP instead. The treatment protocol consisted of three planned cycles of selinexor plus R-GDP regimen. Following this initial phase, patients could receive high-dose chemotherapy followed by ASCT or commercial CD19-targeted chimeric antigen receptor T-cell (CAR-T) therapy, or switch to another treatment regimen based on their response and willingness. Patients eligible for CD19-targeted CAR-T received either axicabtagene ciloleucel or relmacabtagene autoleucel. Prior to CAR-T infusion, patients received lymphodepleting chemotherapy consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day intravenously for 3 consecutive days for axicabtagene ciloleucel and fludarabine 25 mg/m^2/day and cyclophosphamide 250 mg/m^2/day intravenously for 3 consecutive days for relmacabtagene autoleucel. A single infusion of 2 × 10^6 CAR-T cells/kg (axicabtagene ciloleucel) or 100 × 10^6 CAR-T cells (relmacabtagene autoleucel) was administered intravenously two days after completion of lymphodepletion. Patients were monitored in the hospital for at least 10-14 days post-infusion and followed closely for acute toxicities, including cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome. Management included tocilizumab and/or corticosteroids as needed. Response to treatment was assessed using the Lugano 2014 criteria [14]. Patients underwent 18F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) or computed tomography (CT) both prior to and following treatment with selinexor plus R-GDP for the purpose of response assessment. Adverse events (AE) were rated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

Statistical analysis

ORR was defined as the proportion of patients achieving either a complete response (CR) or a partial response (PR), evaluated after 3 cycles of selinexor plus R-GDP. OS was defined as the time from initiation of selinexor plus R-GDP to any cause of death. PFS was defined as the time from the initiation of selinexor plus R-GDP to the first occurrence of disease progression or death from any cause, whichever occurred first. Patients who were still alive and without progression were censored at the date of last follow-up. Descriptive statistics were used to summarize the patient population and clinical outcomes. **Table 1** presents the baseline characteristics of the entire study population; no statistical comparisons between groups were performed for this table. Continuous variables are presented as median with range, and categorical variables are presented as numbers and percentages (n, %). For the time-to-event endpoint, the Kaplan-Meier method was employed to estimate survival rates, which are presented along with their 95% confidence intervals (CI). The differences between the survival curves were compared using the log-rank test. All statistical analyses were performed using R (version 4.4.1) and R Studio (2024-06-14). A two-sided p-value <0.05 was considered statistically significant. In the figures, the p-value resulting from the log-rank test is denoted on the graph.

Results

Patient characteristics

This retrospective analysis included 22 adult patients with relapsed or refractory diffuse

Table 1. Baseline characteristics, treatment regimens, and the responses to first-line therapy of patients (n=22)

Patient characteristics	Number (%)
Median age (range), years	54 (22-69)
Gender	
Male	9 (41)
Female	13 (59)
DLBCL subtype	
GCB	6 (27)
Non-GCB	16 (73)
Double-expression DLBCL	
Yes	5 (23)
No	17 (77)
ECOG PS	
0	3 (14)
1	19 (86)
Lugano staging	
I-II	6 (27)
III-IV	16 (73)
IPI score	
0-2	13 (59)
3-5	9 (41)
Regimens of first-line treatment	
R-CHOP	16 (73)
R2-CHOP	3 (14)
ZR-CHOP	3 (14)
Disease status	
Primary refractory	15 (68)
Relapsed	7 (32)
Response to first-line treatment	
CR	7 (32)
PR	3 (14)
SD	4 (18)
PD	8 (36)

DLBCL: Large B-cell lymphoma; GCB: Germinal center B-cell like; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; R-CHOP: Rituximab, cyclophosphamide, vindesine, doxorubicin, prednisone; R2: Rituximab, lenalidomide; Z: Zanubrutinib; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. Double-expression: a C-MYC protein expression rate exceeding 40% and a BCL-2 protein expression rate exceeding 50% in immunohistochemical analysis.

large B-cell lymphoma (R/R DLBCL) identified from the electronic medical records of our institution between January and August 2023. The stepwise selection process leading to the final analytic cohort is shown in **Figure 1**. The median age of the patients was 54 years (range, 22-69 years). Most patients had an Eastern Cooperative Oncology Group performance status of 1 (86%). A total of 9 (41%) patients had an International Prognostic Index score of 3-5. Six patients (27%) had germinal center B-cell-like (GCB) disease, while 16 patients (73%) had non-GCB disease. Overall, 15 patients (68%) had primary refractory disease, including 8 who experienced disease progression during or immediately after frontline therapy. Of all the patients, 5 patients were double-expression DLBCL. The most common frontline regimen was R-CHOP (rituximab, cyclophosphamide, vindesine, doxorubicin, prednisone; n=16, 73%), followed by zanubrutinib plus R-CHOP (n=3, 14%) and lenalidomide plus R-CHOP (n=3, 14%). Baseline characteristics, treatment regimens, and responses to frontline therapy are summarized in **Table 1**.

Outcomes

All patients received second-line treatment with selinexor plus R-GDP. Seventeen patients completed the planned 3 cycles, while 5 received only 1-2 cycles due to rapid progression (n=2), transition to alternative therapy (n=2), or loss to follow-up (n=1). Among 21 evaluable patients, 11 (52.4%) achieved a response, including 3 CR and 8 PR. In patients with primary refractory disease, the response rate was 40.0% (6/15; 1 CR and 5 PR). Three patients who achieved CR underwent autologous stem cell transplantation (ASCT) and remained in remission at last follow-up. Among the 8 patients with PR, 5 (63%) subsequently received CAR-T therapy; none underwent ASCT. Of the 10 patients with stable or progressive disease, 3 received CAR-T therapy. The ORR for all patients who received CAR-T therapy was 100% (8/8) with 7 CR and 1 PR. For those patients who did not receive ASCT or CAR-T therapy, traditional chemotherapy like R-DHAP or R-MINE (rituximab, mitoxantrone, ifosfamide, etoposide), novel therapy like antibody-drug conjugates (ADCs, i.e. polatuzumab vedotin or loncastuximab tesirine) were used.

At a median follow-up of 25.5 months from initiation of selinexor plus R-GDP (range, 23.4 months-not reached), median overall survival (OS) was 26.9 months (95% CI, 12.1-not reached). The OS rates at 1 year and 2 years were 67.6% (95% CI, 50.5-90.6%) and 52.3% (95% CI, 34.6-79.1%), respectively (**Figure 2A**).

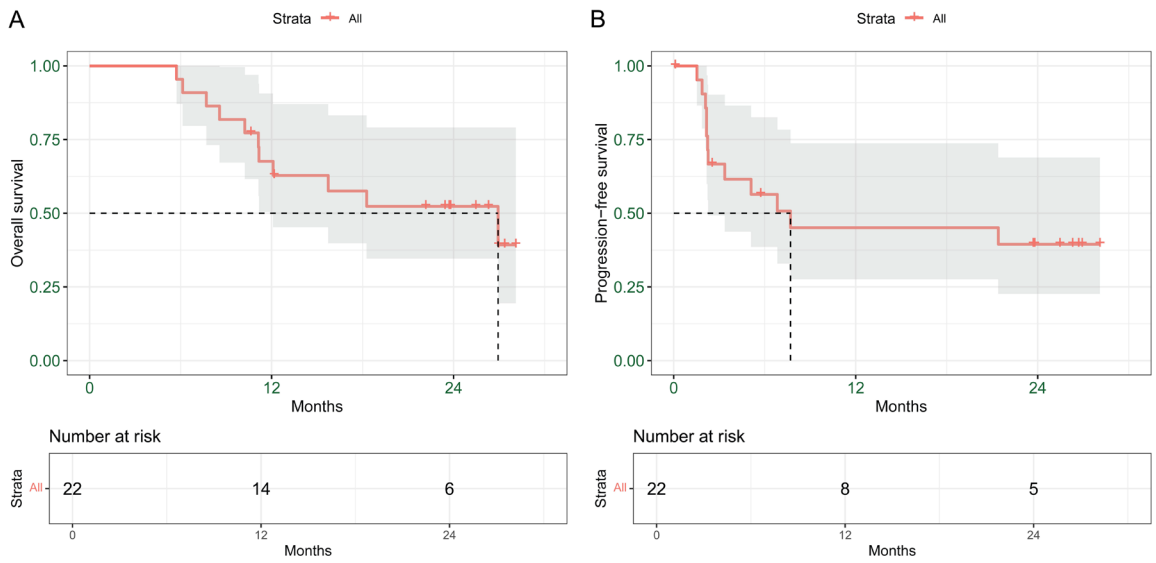

Figure 2. Kaplan-Meier curve for overall survival and progression free survival for all patients (N=22). A. The median OS from selinexor plus R-GDP initiation was 26.9 (95% CI, 12.1 - not reached) for these 22 patients. The OS rates at 1 year and 2 years were 67.6% (95% CI, 50.5-90.6%) and 52.3% (95% CI, 34.6-79.1%), respectively. B. The median PFS from selinexor plus R-GDP initiation was 7.7 (95% CI, 2.27 - not reached) for these 22 patients. The survival estimate was derived using the Kaplan-Meier method. As this analysis describes a single cohort, no statistical test for comparison was applied. Tick marks on the curve indicate censored observations. The corresponding number of patients at risk over time is presented below the plot. OS: Overall survival; PFS: Progression free survival; R-GDP: Rituximab, gemcitabine, dexamethasone, and cisplatin; CI: Confidence intervals.

OS differed significantly by subsequent treatment (*P*=0.0217; **Figure 3A**): median OS was not reached in the ASCT group, 26.9 months (95% CI, 15.9-not reached) in the CAR-T group, and 11.2 months (95% CI, 10.2-not reached) in patients receiving other therapies. No OS difference was observed between primary refractory and relapsed patients (*P*=0.2323; **Figure 3B**). Median progression-free survival (PFS) was 7.7 months (95% CI, 2.27-not reached) for the entire cohort (**Figure 2B**). PFS differed significantly by subsequent therapy (*P*=0.0029; **Figure 3C**): median PFS was not reached for patients undergoing ASCT or CAR-T, compared with 2.2 months (95% CI, 2.1-not reached) for others. Patients with relapse after frontline therapy had longer median PFS than those with primary refractory disease (not reached vs 2.82 months [95% CI, 2.17-not reached]; *P*=0.0072; **Figure 3D**).

Safety

The most frequent treatment related adverse events (TRAEs ≥20%) were thrombocytopenia (100%), fatigue (59%), neutropenia (45%), anemia (45%), and pneumonia (23%). Grade 3-4 hematologic toxicities included neutropenia in 6 (27%) patients, thrombocytopenia in 7 (32%) patients. These occurrences were managed with routine supportive care or dose interruption. No AEs leading to death were observed. All five patients with grade 3 pneumonia were graded as serious adverse events (SAEs) with associated hospital admission or prolonged hospitalization.

Discussion

We evaluated the efficacy and safety of selinexor combined with R-GDP as a second-line salvage regimen and described subsequent treatments and outcomes. Overall, the ORR was 52.4%, and the median OS was 26.9 months. Notably, among the 22 patients with R/R DLBCL, the 1-year and 2-year OS rates were 67.6% and 52.3%, respectively. Of note, OS differed significantly according to subsequent therapy, including ASCT, CAR T-cell therapy, or other treatments. The most frequently reported adverse events were thrombocytopenia, fatigue, neutropenia, anemia, and pneumonia.

The ORR and CR rate observed in our retrospective study (52.4% and 14.3%, respectively) in R/R DLBCL patients receiving selinexor plus R-GDP were modest and slightly lower than

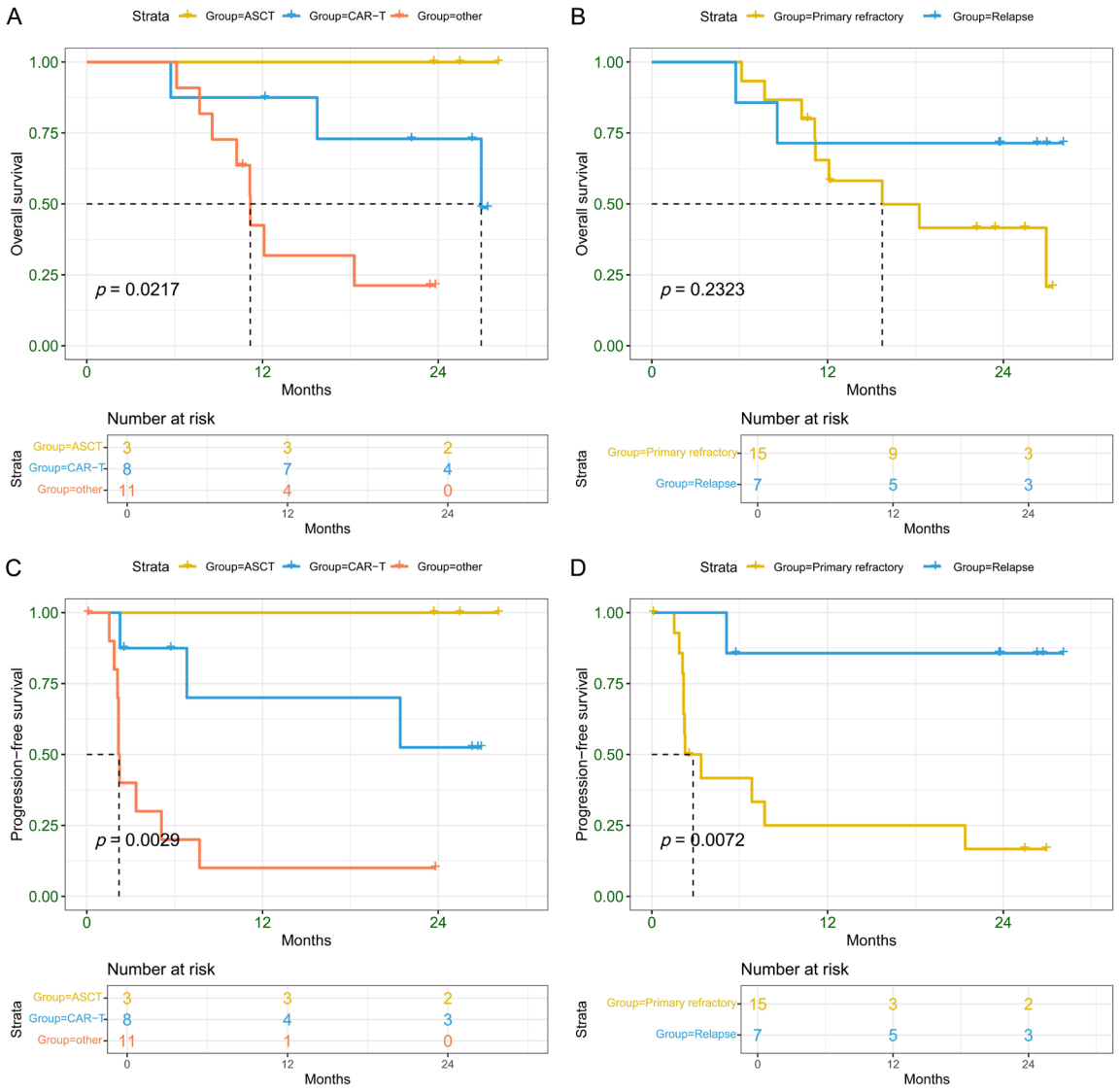

Figure 3. Kaplan-Meier curve for overall survival and progression free survival in patient subgroups. (A) OS and (C) PFS based on the type of subsequent therapy received after selinexor plus R-GDP: ASCT, CAR-T, or other treatments. (B) OS and (D) PFS based on the response to front-line therapy: primary refractory or relapsed disease. Tick marks on the curve indicate censored observations. The corresponding number of patients at risk over time is presented below the plot. The survival estimate was derived using the Kaplan-Meier method, and the associated *p*-value is from the log-rank test. *p*-value <0.05 was considered statistically significant. OS: Overall survival; PFS: progression free survival; R-GDP: Rituximab, gemcitabine, dexamethasone, and cisplatin; ASCT: Autologous stem cell transplantation; CAR-T: Chimeric antigen receptor T-cell.

the 60% ORR and 26.7% CR reported in the SELINDA study [10], which employed the same regimen and recommended dosing schedule. Notably, a key distinction lies in baseline patient characteristics: the proportion of primary refractory disease was substantially higher in our cohort (68%) compared with the SELINDA study (33%). In addition, our analysis was restricted to DLBCL, whereas the SELINDA cohort also included follicular lymphoma and marginal zone lymphoma. Although our patients were younger (median age, 54 vs. 61 years) and had a similar frequency of advanced-stage disease, the higher burden of truly refractory patients in our study likely contributed to the lower ORR and CR rates observed. Importantly, these cross-trial comparisons are inherently limited by their non-randomized design and should be interpreted with caution.

When compared to other traditional chemotherapy regimens as salvage treatment, the

response rate of our study was similar to that of the R-GDP/GDP regimens [5, 15, 16], but lower than that observed with other intensified chemotherapies, such as R-ICE, R-DHAP, R-DICEP (rituximab, cyclophosphamide, etoposide, and cisplatin), R-IVAD (rituximab, ifosfamide, etoposide, cytarabine, and dexamethasone), and R-ESHAP (rituximab, etoposide, methylprednisolone, cytarabine, and cisplatin) [6, 15, 17-19]. The difference in ORR may be attributable to the fact that some prior studies included patients who had not been exposed to rituximab in the frontline setting, whereas all patients in our study had relapsed or refractory disease following rituximab-containing therapy, with a refractory rate as high as 68%. Notably, these intensified chemotherapies usually had more serious adverse events or higher rates of grade 3-5 toxicities and used in more fit patients. In our study, only 14% of patients underwent ASCT, compared with ~50% reported with traditional chemotherapy, likely because patients achieving only PR did not proceed to transplantation. We believe with the approval of emerging therapies, such as polatuzumab vedotin (an anti-CD79b ADC) and epcoritamab or glofitamab (bispecific antibodies targeting CD3 and CD20) in China [20-22], the survival outcomes of R/R DLBCL are likely to be further improved.

An important observation from our study is that patients with a PR response rarely proceeded to ASCT; instead, most opted for CAR-T therapy, which was associated with comparable ORR and survival to ASCT but significantly better outcomes than alternative therapies (P=0.0217). Given that prior studies have demonstrated inferior long-term outcomes for patients undergoing ASCT with only a PR, our findings support CAR-T as a more effective option for this subgroup [23-25]. Actually, CAR-T therapy has revolutionized the treatment landscape in the past few years. More than three anti-CD19 CAR-T products have been approved for use in patients with R/R DLBCL after two or more prior lines of therapy [26]. Two phase 3 trials demonstrated that anti-CD19 CAR-T products (axicabtagene ciloleucel and lisocabtagene maraleucel) confer superior response rates and survival compared with salvage chemoimmunotherapy ± high-dose chemotherapy followed by ASCT [27, 28]. Accordingly, the ASTCT Committee recommends anti-CD19 CAR-T for patients with primary refractory or early relapsed (≤12 months) disease, and ASCT for those with late relapse (>12 months) [29]. In our retrospective analysis, most patients with a PR after salvage therapy chose CAR-T over ASCT, which was associated with improved long-term survival. This observation suggests a potentially promising therapeutic algorithm favoring CAR-T in PR patients; however, prospective studies are required to directly compare CAR-T and ASCT in this setting.

This study is limited by its retrospective design, which may introduce selection bias and affect the interpretation of the results. Therefore, caution should be exercised when comparing our findings, particularly since the ORR was lower than that reported in the SELINDA study. Additionally, some adverse events, such as gastrointestinal toxicities, were documented in the SELINDA study but not observed in our analysis, possibly reflecting underreporting of mild events in medical records. Besides, the lack of a control group precludes assessment of relative efficacy, and meaningful propensity score matching was not feasible due to limited treatment distribution. Similarly, multivariable Cox regression could not be performed given the small sample size and event rate. The single-center nature of this study may also limit generalizability. Nevertheless, our findings provide real-world evidence supporting selinexor plus R-GDP as a salvage option for R/R DLBCL and highlight a potential treatment algorithm for transplant-eligible patients achieving PR.

In conclusion, this retrospective study demonstrates the efficacy and safety of selinexor plus R-GDP as salvage therapy for R/R DLBCL in a real-world setting, albeit with modest response rates. Patients achieving CR should proceed to ASCT, whereas those with PR may derive greater benefit from CAR-T therapy. Further prospective, multicenter studies are warranted to define the optimal sequencing of ASCT and CAR-T therapy in this population.

Acknowledgements

The authors would like to thank the patients who consented to their data to being used anonymously for this study.

Disclosure of conflict of interest

None.

Abbreviations

R/R, Relapsed or refractory; DLBCL, Diffuse large B-cell lymphoma; R-GDP, Rituximab, gemcitabine, dexamethasone, and cisplatin; ASCT, Autologous stem cell transplantation; CAR-T, Chimeric antigen receptor T-cell; ORR, Overall response rate; OS, Overall survival; CI, Confidence intervals; R-DHAP, Rituximab, dexamethasone, high-dose cytarabine, and cisplatin; R-ICE, Rituximab, ifosfamide, carboplatin, and etoposide; SINE, Selective inhibitor of nuclear export; FDA, Food and Drug Administration; DOR, Duration of response; R2, Rituximab-lenalidomide; PFS, Progression-free survival; PET/CT, Positron emission tomography/computed tomography; CT, Computed tomography; AE, Adverse events; CR, Complete response; PR, Partial response; GCB, Germinal center B-cell like; R-CHOP, Rituximab, cyclophosphamide, vindesine, doxorubicin, prednisone; R-MINE, Rituximab, mitoxantrone, ifosfamide, etoposide; ADCs, Antibody-drug conjugates; TRAEs, Treatment related adverse events; SAEs, Serious adverse events; R-DICEP, Rituximab, cyclophosphamide, etoposide, and cisplatin; R-IVAD, rituximab, ifosfamide, etoposide, cytarabine, and dexamethasone; R-ESHAP, Rituximab, etoposide, methylprednisolone, cytarabine, and cisplatin; R-DHAX/C, Rituximab, dexamethasone, cytarabine, and oxaliplatin/carboplatin; ASTCT, American Society of Transplantation and Cellular Therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; Z, Zanubrutinib; SD, Stable disease; PD, Progressive disease.

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