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Real-world efficacy of chidamide plus R-CHOP in newly diagnosed double-expressor diffuse large B-cell lymphoma

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Abstract

Background: Approximately 20%–30% of diffuse large B-cell lymphoma (DLBCL) cases are classified as double-expressor lymphoma (DEL), characterized by the co-expression of the MYC and BCL2 proteins. However, the most effective therapeutic strategy for DEL remains unidentified.

Objectives: To evaluate the efficacy of a novel histone deacetylase inhibitor, chidamide, in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (CR-CHOP) in the treatment of DEL.

Design: This was a retrospective study.

Methods: This study included 62 DEL patients from December 2016 to December 2020. All patients were administered a first-line treatment with CR-CHOP. The short-term efficacy, survival status, and adverse reactions in this population were observed, and the prognostic factors were analyzed.

Results: The median age was 53.9 years (range, 19–77). All patients received a median of six cycles (range, 1–8) of treatment, with 79.0% achieving complete response (CR) and an overall response rate of 88.7%. With a median follow-up of 45.5 months (range, 1–82), the median progression-free survival (PFS) and median overall survival (OS) had not yet been reached. However, the 3-year PFS rate was 71% (95% CI: 61–83), the 3-year OS rate was 87% (95% CI: 79–96), the 5-year PFS rate was 67% (95% CI: 55–80), and the 5-year OS rate was 85% (95% CI: 77–95). Age and autologous stem cell transplantation after CR or partial response were independent prognostic factors for PFS, while various clinical factors were not associated with OS outcomes. The most common grades 3–4 hematologic and nonhematologic toxicity were leukopenia (46.7%) and infection (21%), respectively.

Conclusion: This long-term follow-up study indicates that CR-CHOP in untreated DLBCL with the DEL phenotype demonstrates high short-term efficacy and safety as well as promising survival outcomes.

Keywords: chidamide, diffuse large B-cell lymphoma, double-expressor lymphoma, first-line, histone deacetylase inhibitor

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of aggressive lymphoma, accounting for 30%–40% of non-Hodgkin's lymphomas.[1] DLBCL has a *MYC* rearrangement, which can occur in conjunction with a *BCL2* or *BCL6* rearrangement. These are referred to as "double-hit" (DH) or "triple-hit" (TH) lymphomas and have been identified as poor prognostic factors.[2,3] Even in the absence of gene

rearrangements of DH/TH, expression of MYC and BCL2 proteins has been identified by immunohistochemistry (IHC) in some patients with DLBCL. According to the revised 2016 World Health Organization (WHO) classification, a cutoff value of 40% for MYC and a threshold value of 50% for BCL2 protein expression are recommended.[4] In DLBCL, the expression of MYC and BCL2 proteins is 30%–50% and 20%–35%, respectively. Co-expression of the two has been described as a double-expressor lymphoma (DEL) with an incidence of 20%–30%, which is more common than DH/TH in clinical practice.[5]

DEL continues to exhibit unique clinical phenotypes. These include a higher prevalence of non-germinal center B-cell (non-GCB) subtypes, a higher Ki-67 proliferative index, intermediate/high-risk to high-risk International Prognostic Index (IPI) scores, involvement of multiple extranodal sites, and more advanced disease.[6] All of these factors are associated with an aggressive clinical course. DEL has a poor prognosis with conventional R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) treatment. The 5-year progression-free survival (PFS) is only 27%–32%, and the 5-year overall survival (OS) is 30%–36%.[7,8] Even with DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) intensive chemotherapy regimens, no survival benefit has been observed.[9] Therefore, clinicians are exploring more effective ways to improve survival in DEL patients. Novel agents in combination with R-CHOP have shown improved clinical outcomes in DLBCL.

Chidamide is an innovative histone deacetylase (HDAC) inhibitor that targets both class I HDACs (HDAC1, HDAC2, and HDAC3) and class IIb HDACs (HDAC10).[10] Chidamide has been shown to overcome rituximab-induced CD20 downregulation and synergize its mediated cytotoxicity.[11] It is also used to overcome acquired resistance to chemotherapy in aggressive B-cell lymphomas.[12] As a result, chidamide has emerged as a promising therapeutic option for the treatment of B-cell lymphomas in recent years. Study have reported favorable efficacy of chidamide in combination with rituximab in the treatment of relapsed/refractory DLBCL in the elderly, with an overall response rate (ORR) of 40%.[13] Moreover, chidamide combined with R-CHOP (CR-CHOP) has shown positive efficacy and a manageable safety profile in the treatment of elderly DLBCL patients as a first-line treatment regimen. It has also shown encouraging efficacy in a very small sample of DEL patients.[14] Based on the interim analysis results of an unpublished phase III clinical study, the combination of chidamide and R-CHOP has been officially approved for treating newly diagnosed DLBCL with MYC and BCL2 expression. The present single-center retrospective analysis evaluated the short-term effectiveness and safety of this treatment and performed long-term follow-up of patients diagnosed with DLBCL DEL subtype who were treated with CR-CHOP.

Materials and methods

Patients

The study included DLBCL patients with concurrent MYC and BCL2 expression who were treated at the West China Hospital of Sichuan University. Primary central nervous system lymphoma cases were excluded. All patients were treated with the CR-CHOP regimen as their first-line treatment. All cases were diagnosed according to the WHO Classification of hematopoietic and lymphoid neoplasms. MYC and BCL2 expression were visualized using IHC staining, with cutoff values of 40% and 50%, respectively. The pathologic diagnosis and MYC and BCL2 expression were confirmed by lymphoma specialists.

The treatment regimen was documented in detail in this study. Clinical and laboratory data were collected at the time of diagnosis. Imaging studies, including computed tomography (CT) or magnetic resonance imaging of all body regions, as well as positron emission tomography/CT scans, were used for staging and efficacy assessments. The study also examined whether autologous stem cell transplantation (ASCT) was performed at the end of treatment.

Treatment

The CR-CHOP regimen was administered every 21 days. Rituximab (375 mg/m^2, intravenously on day 0), cyclophosphamide (750 mg/m^2 intravenously on day 1), vincristine (1.4 mg/m^2, maximum 2.0 mg, intravenously on day 1), doxorubicin

(50 mg/m^2 intravenously on day 1), and prednisone (60 mg/m^2 orally on days 1–5) were administered at the usual doses each cycle. Thirty-seven (59.7%) patients were administered 20 mg twice per week (biw) for 2 weeks, followed by a 1-week withdrawal period. Three (4.8%) patients followed the same dosing regimen but with 30 mg of biw; 20 (32.3%) patients were administered 20 mg of biw continuously, and 1 (1.6%) patient took 30 mg of biw continuously.

When grade 3 or higher hematologic or nonhematologic adverse reactions occurred, dosing was suspended, and aggressive symptomatic management was implemented until the adverse reactions reached grade 1 or lower. Prophylactic leukocyte boosting with long- or short-acting granulocyte colony-stimulating factor (G-CSF) was required at the end of the next cycle of the R-CHOP infusion in cases of grade 3 or higher neutropenia. For patients at high risk of central nervous system recurrence, sheath infusion was also considered during the course of treatment. Patients who achieved a complete response (CR) or partial response (PR) at the end of the first-line treatment with CR-CHOP underwent ASCT based on physician recommendations and the patient's decision.

Efficacy and toxicity evaluation

The final response outcome is assessed using the imaging examination after the last cycle of CR-CHOP treatment. The treatment efficacy was assessed using Lugano's (2014 version) response criteria for malignant lymphoma. These criteria include CR, PR, stable disease (SD), and disease progression (PD).[15] The ORR was defined as the proportion of patients with CR or PR. OS was defined as the time from initial diagnosis to death or last follow-up. PFS was defined as the time from diagnosis to disease relapse, progression, or disease-related death.

Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All toxicity data were obtained from physical examinations and blood tests, including complete blood count, liver and kidney function tests, and treatment-related clinical symptoms. Toxicity was described as the highest grade observed in each patient.

Statistical analysis

Statistical analysis was performed using the R language (version 4.3.0). The Shapiro–Wilk test was used to categorize continuous variables as either having a normal or non-normal distribution. Normally distributed variables were presented as mean and standard deviation, while non-normally distributed variables were shown as median with interquartile spacing. Categorical variables were reported as frequencies and percentages, and Fisher's exact test was used to compare groups. OS and PFS were calculated using Kaplan–Meier analysis, and the impact of different grouping factors on patient OS and PFS was analyzed using log-rank tests. Multivariate analysis was conducted using the Cox proportional hazards regression model. A two-sided p value less than 0.05 was considered statistically significant.

Results

Clinical characteristics

From December 2016 to December 2020, a total of 62 patients were included in the study, and Table 1 summarizes the main clinical characteristics. The median age was 53.9 years (range, 19–77), with 30 (48.4%) being male. Out of the total patients, 54 (87.1%) patients were in good physical condition, with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1. B symptoms were present in 21 (33.9%) patients. In terms of disease stage, 39 (62.9%) patients were classified as late stage III–IV according to the Ann Arbor classification. Based on IPI scores, 33 (53.2%) patients were categorized as low/low-medium risk (0–2) and 29 (46.8%) as medium-high/high risk (3–4). Regarding pathological features, 49 (81.7%) patients had a Ki-67 index $\geqslant$80%. Regarding cell-of-origin (COO) classification subtypes, 21 (33.9%) patients had a germinal center B-cell (GCB) profile, while 41 (66.1%) had a non-GCB profile. Among the patients, 29 (46.8%) received a concurrent lumbar puncture sheath injection of cytarabine and/or methotrexate, and a total of 18 (29.0%) patients who achieved CR or PR at the end of first-line treatment underwent ASCT.

Table 1. Clinical characteristics of 62 patients with DLBCL DEL phenotype.

Characteristics	Number (%)
Age (years)	
Mean ± SD	53.9 ± 12.0
<60	39 (62.9)
⩾60	23 (37.1)
Sex	
Female	32 (51.6)
Male	30 (48.4)
ECOG PS	
0–1	54 (87.1)
2–3	8 (12.9)
Ann Arbor stage	
I–II	23 (37.1)
III–IV	39 (62.9)
Extranodal involvement	
Without	9 (14.5)
With	53 (85.5)
Serum LDH	
Normal	35 (56.4)
Elevated	27 (43.6)
B symptom	
Without	41 (66.1)
With	21 (33.9)
IPI score	
0–2	33 (53.2)
3–4	29 (46.8)
Cell-of-origin	
GCB	21 (33.9)
Non-GCB	41 (66.1)
Ki-67 index*	
<80%	11 (18.3)
⩾80%	49 (81.7)
Bulkly (⩾7.5 cm)	
Without	48 (77.4)
With	14 (22.6)
Chidamide dosage	
30 mg biw, 2 weeks, rest a week	3 (4.8)
30 mg biw, continuously	1 (1.6)
20 mg biw, 2 weeks, rest a week	37 (59.7)
20 mg biw continuously	20 (32.3)
15 mg biw, continuously	1 (1.6)
Intrathecal injection	
No	33 (53.2)
Yes	29 (46.8)
ASCT	
No	44 (71.0)
Yes	18 (29.0)

*Was not available for two patients.
ASCT, autologous hematopoietic stem cells; biw, twice per week; DEL, double-expressor lymphoma; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell subtype; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

Treatment and response

The median number of the CR-CHOP regimen was six cycles (range, 1–8) in 62 patients, with 1 patient completing four cycles of treatment and switching to another regimen because of intolerance of side effects, and 51 (82.3%) completing six cycles or more. Ultimately, 49 (79.0%) achieved CR, 6 (9.7%) achieved PR, 1 (1.6%) showed SD, and 6 (9.7%) exhibited PD in 62 patients. The ORR was 88.7% (95% CI: 78.11–95.34).

When comparing the treatment responses among different groups, we found that treatment was more effective for patients under 60 years compared to those over 60 years (97.4% vs 73.9%,

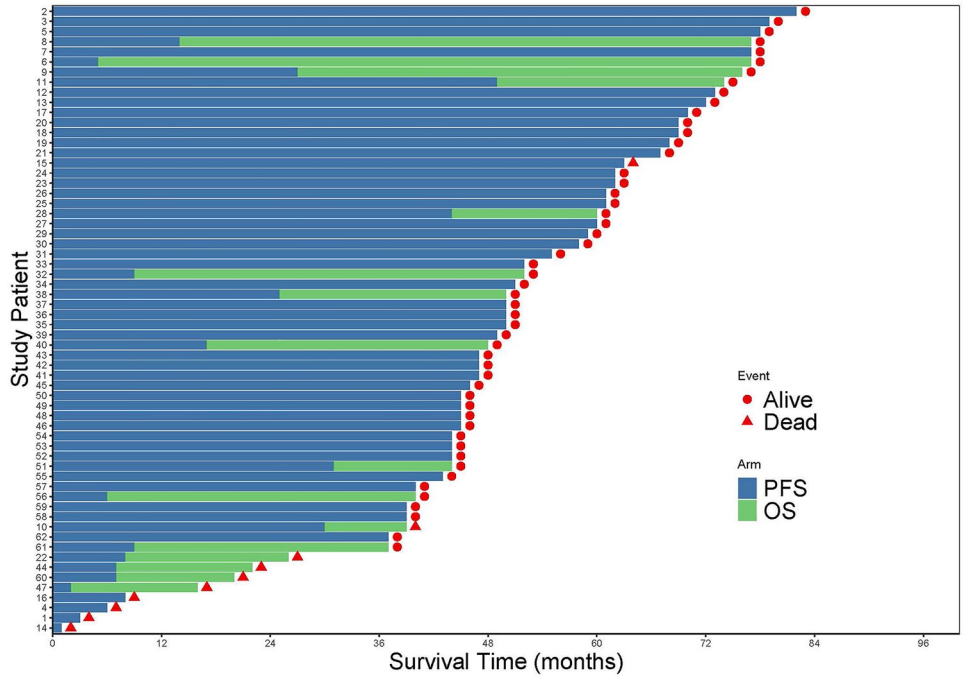

Figure 1. Swim plot illustrating survival status, PFS, and OS durations for each patient.
PFS, progression-free survival; OS, overall survival.

$p = 0.020$). Patients without B symptoms also demonstrated better responses compared to those with B symptoms (95.1% vs 76.2%, $p = 0.042$). Furthermore, the non-GCB group exhibited a better treatment response than the GCB subgroup (95.1% vs 76.2%, $p = 0.042$). However, there was no statistically significant difference in the likelihood of ORR outcomes among subgroups, based on disease staging, IPI, and Ann Arbor stage (Supplemental Figure S1).

Survival outcomes

The swimmer plot shown in Figure 1 provides specific information on the recurrence and survival results of the 62 patients, offering a visual representation of the individual response patterns observed. As of the time this article was written, there have been 17 relapses and 10 deaths have also occurred, all attributed to treatment failure.

With a median follow-up of 45.5 months (range, 1–82), the median PFS and OS in the total population has not yet been reached. However, the 3-year PFS was 71% (95% CI: 61–83), 3-year OS was 87% (95% CI: 79–96), 5-year PFS was 67% (95% CI: 55–80), and 5-year OS was 85% (95% CI: 77–95; Figure 2).

Furthermore, based on the Ann Arbor staging subgroup analysis, early-stage patients (stage I–II) had a 3-year PFS rate of 91% (95% CI: 80–100), contrasting with the 59% (95% CI: 45–77) observed for advanced-stage patients (III–IV). The 5-year PFS rate was 86% (95% CI: 72–100) for early-stage patients and 56% (95% CI: 42–74) for advanced-stage patients. The difference in PFS between the two groups was statistically significant ($p = 0.006$). Notably, there were no deaths among early-stage patients at the final follow-up date of the study, resulting in a 5-year OS rate of 100% (95% CI: 100–100). For advanced-stage patients, the 3- and 5-year OS rates were 79% (95% CI: 68–93) and 77% (95% CI: 65–91), respectively. Patients in earlier stages had better OS ($p = 0.0096$; Figure 3(a)).

According to the IPI score subgroup analysis, low/low-to-intermediate risk patients (IPI 0–2) had a higher 3-year PFS rate of 85% (95% CI: 73–98) compared to 55% (95% CI: 40–77) for intermediate-to-high/high-risk patients (IPI

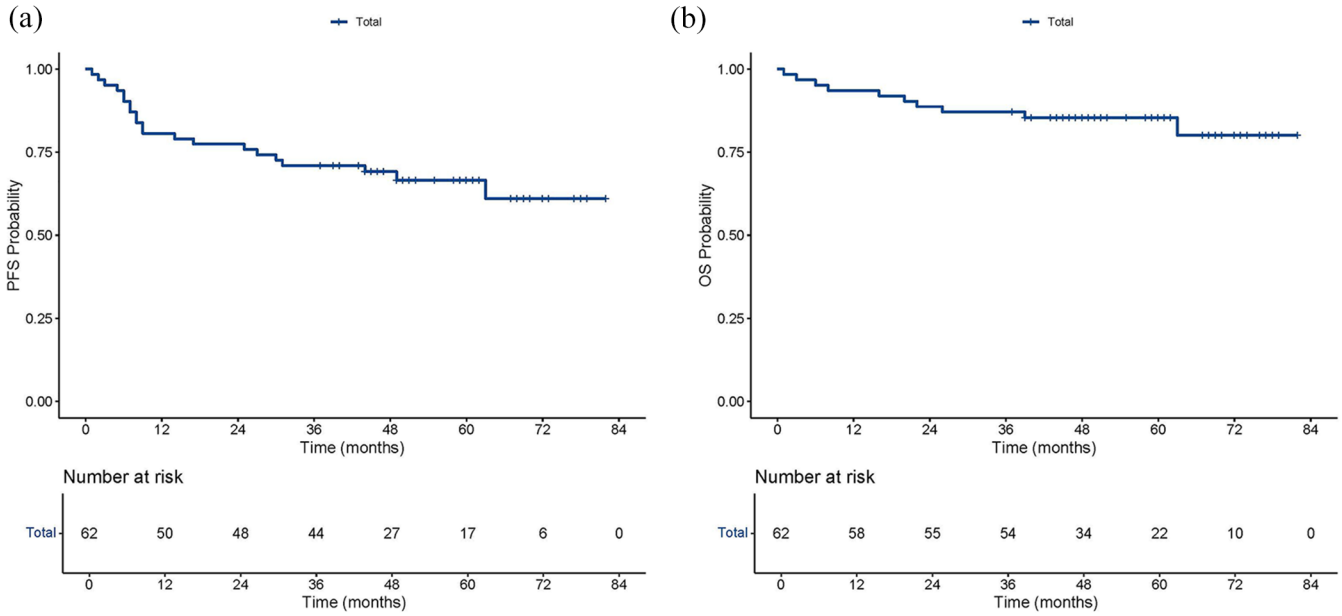

Figure 2. Survival outcomes for the total population: (a) PFS and (b) OS.
PFS, progression-free survival; OS, overall survival.

3–4). The 5-year PFS rates were 81% (95% CI: 68–96) and 51% (95% CI: 36–73) respectively, with a significant difference ($p = 0.003$). The 3-year OS rates were 94% (95% CI: 86–100) for low/low-to-intermediate risk patients and 79% (95% CI: 66–96) for intermediate-to-high/high-risk patients. The 5-year OS rates were 94% (95% CI: 86–100) and 76% (95% CI: 62–93) respectively, with low/low-to-intermediate risk patients showing better OS ($p = 0.022$; Figure 3(b)).

According to the ASCT subgroup analysis, patients who underwent transplantation had a higher 3-year PFS rate of 89% (95% CI: 75–100) compared to 64% (95% CI: 51–80) for patients without transplantation. The 5-year PFS rate was 89% (95% CI: 75–100) for patients who underwent ASCT and 58% (95% CI: 45–75) for patients who did not. Patients who underwent ASCT also had better PFS ($p = 0.025$). The 3-year OS rate was 100% (95% CI: 100–100) for patients who underwent ASCT and 82% (95% CI: 71–94) for patients who did not. The 5-year OS rate was 100% (95% CI: 100–100) for patients who underwent ASCT and 79% (95% CI: 68–92) for patients who did not. Overall, patients who underwent ASCT had better OS ($p = 0.038$; Figure 3(c)).

In the age <60 group, the PFS was better compared to the ⩾60 group ($p = 0.012$), with a 3-year PFS of 82% (95% CI: 71–95) versus 52% (95% CI: 35–77) and a 5-year PFS of 79% (95% CI: 67–93) versus 46% (95% CI: 29–73), respectively. However, no notable variance was observed in OS (Figure 3(d)). Additionally, baseline metrics such as COO classification exhibited no discernible discrepancies in either PFS or OS across subgroups (Supplemental Figures S2 and S3).

Prognostic factors

To explore the correlations between the clinical variables and survival of DEL patients, we conducted a Cox regression multivariable analysis using all the variables that had previously shown significance in the univariable analysis. The analysis aimed to identify possible independent predictors for PFS and OS. The results showed that age and ASCT were independent prognostic factors for PFS. Patients aged ⩾60 had a 3.36 times higher risk of disease progression or death compared to patients aged <60 (hazard ratio [HR]: 3.36, 95% CI: 1.07–10.56, $p = 0.038$). Furthermore, patients who underwent ASCT had 0.16 times the risk of disease progression or death compared to those who did not (HR: 0.16, 95% CI: 0.03–0.78, $p = 0.024$). However, none of

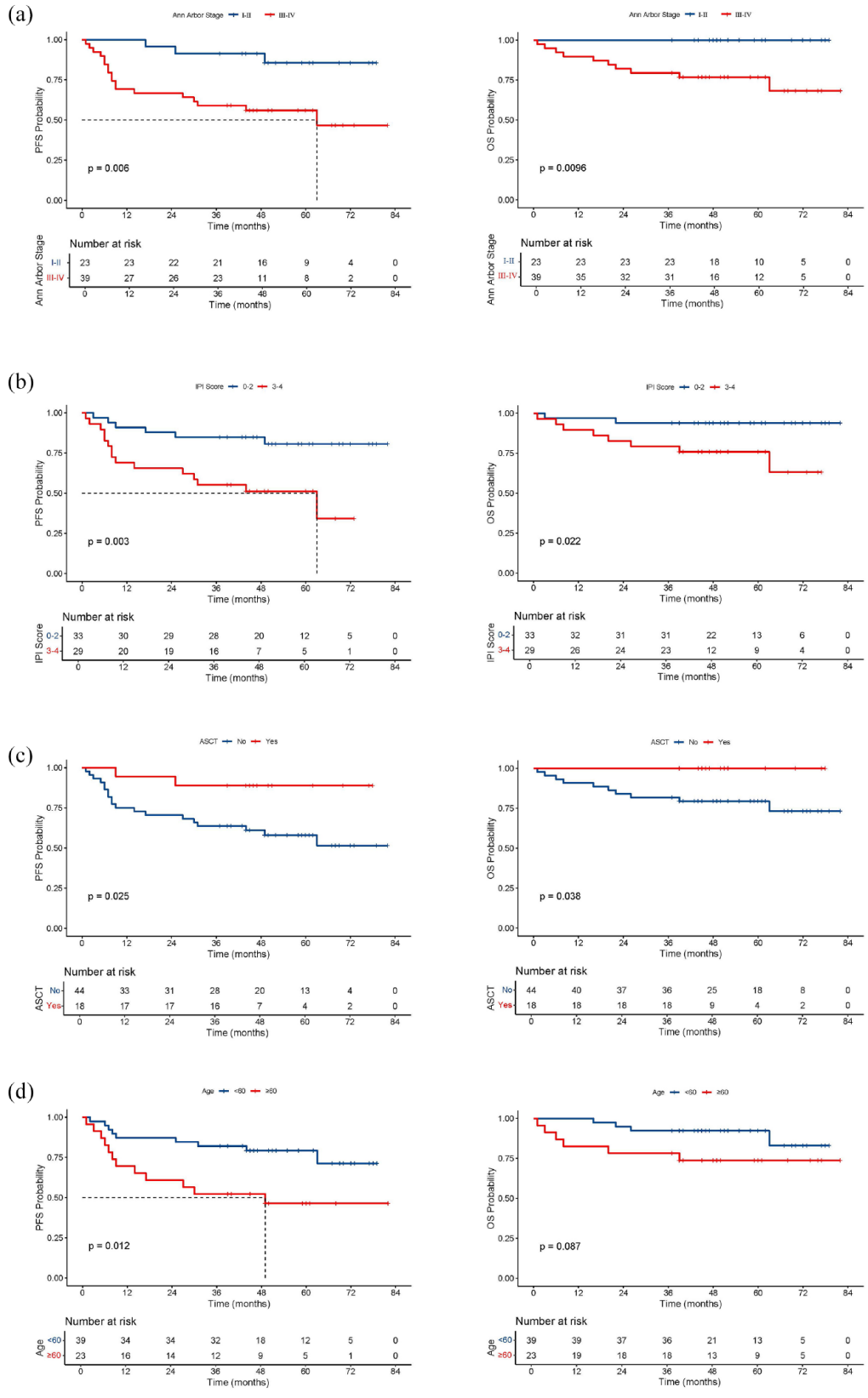

Figure 3. Survival outcomes for subgroups. (a) PFS and OS based on Ann Arbor stages; (b) PFS and OS based on IPI scores; (c) PFS and OS based on ASCT status; (d) PFS and OS based on age.
ASCT, autologous stem cell transplantation; IPI, International Prognostic Index; PFS, progression-free survival; OS, overall survival.

the factors included in the multifactorial analysis were associated with the likelihood of OS.

Toxicity

Table 2 provides a list of treatment-related adverse events (TRAEs), and no deaths attributed to TRAEs were reported. The most frequently observed grade 3–4 hematologic AEs were decreased neutrophil counts (46.7%), granulocyte deficiency with fever (19.4%), anemia (16.1%), and decreased platelet counts (11.3%). The most common nonhematologic AE was infection (30.7%), with 21% being grade 3. The respiratory tract was the most prevalent site. The causative pathogens could not be identified in seven cases. Among patients with confirmed pathogens, seven cases involved opportunistic infections, including those caused by fungi, herpesvirus, and mycobacteria, which occurred alone or in combination with bacterial infections, leading to dual or even triple infections. The next most common grade 3–4 nonhematologic AE was abnormal liver function, which encompassed elevated alanine aminotransferase (ALT) (4.8%) and aspartate aminotransferase (AST) (4.8%) levels. Severe grade 4 toxicity occurred in 21 cases, including 19 cases of neutropenia, 1 case of thrombocytopenia, and 1 case of significantly elevated AST, all of which resolved with treatment. The first occurrence of grade 3–4 neutropenia and subsequent treatment with prophylactic leukocytosis with G-CSF resulted in a significant reduction in severe neutropenia. The incidence of rash was 6.4%, reaching grade 3 in only one case, which led to a change in regimen after four cycles due to intolerance. Other rare toxicities, all of which were mild (grade 2 or less), included fatigue (8.0%), abdominal pain or diarrhea (8.0%), neuropathy (6.5%), and cardiovascular disease (1.6%).

Discussion

The treatment of patients with newly diagnosed DLBCL DEL subtype with CR-CHOP CRR of 79.0% and an ORR of 88.7%. This treatment approach also led to a 3-year PFS of 71%, a 3-year OS of 87%, a 5-year PFS of 67%, and a 5-year OS of 85% for all patients, with a median follow-up of 45.5 months. These results demonstrate promising efficacy and favorable survival outcomes.

DLBCL patients with MYC/BCL2 co-expression have a poorer prognosis and a high-risk gene expression profile. Various studies have highlighted the importance of assessing MYC and BCL2 protein expression in determining the prognosis and guiding treatment for DLBCL, particularly in patients with the double-expressor phenotype.[5,7,8] However, limited information is available regarding the optimal treatment for patients with the DEL phenotype of DLBCL in clinical practice. Traditional R-CHOP therapy has shown poor efficacy as a first-line treatment for the DEL subtype, with a 2-year PFS rate of 58% and a 2-year OS rate of 75% in patients with advanced DLBCL participating in the trial by Persky et al.[16] Meanwhile, a study by Johnson et al.[5] reported a 5-year PFS rate of 32% and a 5-year OS rate of 36% in 55 patients. Moreover, in a larger sample of 157 patients, the 5-year PFS and OS rates were 27% and 30%, respectively.[8] Unfortunately, even the intensive chemotherapy regimen R-DA-EPOCH failed to improve the poor prognostic outcomes for DEL patients in terms of both PFS and OS.[9] These findings indicate a need for improved therapeutic approaches in patients with the DEL phenotype.

Novel agents known as HDAC inhibitors, when used in combination with R-CHOP, have shown potential for improving clinical outcomes in DEL phenotype DLBCL. A phase I/II study comparing vorinostat in combination with R-CHOP to R-CHOP alone showed improved prognoses in DEL patients, with a 2-year PFS rate of 73% versus 58% and a 2-year OS rate of 91% versus 75%.[16] Additionally, in a study evaluating CR-CHOP for DLBCL in elderly patients with an IPI $\geq$ 2, all 12 DEL phenotype patients achieved CR, with 2-year PFS and OS rates of 83% and 92%, respectively, demonstrating superior treatment responses compared to the overall patient population.[14] Therefore, drugs targeting histone deacetylation may offer enhanced benefits for DEL patients.

In recent years, chidamide, a novel HDAC inhibitor, has emerged as a promising therapeutic option for the treatment of B-cell lymphoma. Chidamide seems to trigger cell death through autophagy activation, particularly in the absence of pro-apoptotic proteins. It is also involved in inducing G0/G1 cell cycle arrest, inhibiting cell growth, and overcoming resistance to multiple

Table 2. Hematological and nonhematological adverse events.

Adverse events	Grades 1–2	Grades 3	Grades 4
Hematologic			
Neutropenia	13 (21.0%)	10 (16.1%)	19 (30.6%)
Anemia	38 (61.3%)	10 (16.1%)	0 (0%)
Thrombocytopenia	18 (29.0%)	6 (9.7%)	1 (1.6%)
Febrile neutropenia	0 (0%)	12 (19.4%)	0 (0%)
Nonhematologic			
Increased alanine aminotransferase	16 (25.8%)	3 (4.8%)	0 (0%)
Increased aspartate aminotransferase	17 (27.4%)	2 (3.2%)	1 (1.6%)
Increased creatinine	4 (6.5%)	0 (0%)	0 (0%)
Infection	6 (9.7%)	13 (21.0%)	0 (%)
Cardiac	1 (1.6%)	0 (%)	0 (%)
Abdominal pain or diarrhea	5 (8.0%)	0 (%)	0 (%)
Fatigue	5 (8.0%)	0 (%)	0 (%)
Neurological	4 (6.5%)	0 (%)	0 (%)
Skin rash	3 (4.8%)	1 (1.6%)	0 (%)

chemotherapeutic agents.[12] Moreover, chidamide may counteract rituximab-mediated CD20 downregulation, thereby enhancing the effectiveness of rituximab.[11] In vitro assays have also found that chidamide can suppress the c-MYC protein in DLBCL cell lines, irrespective of the *MYC* gene's rearrangement status. It can also synergistically increase the level of pro-apoptotic proteins, thereby reducing the expression of BCL2.[17] In this context, chidamide's effect on levels of key proteins may offer a strategy to improve drug resistance in DLBCL treatment.

MYC/BCL2 co-expression is associated with high-risk clinical parameters, leading to a poorer overall prognosis in patients with DEL. In our study, we found that the Ki-67 proliferative index reached 80% or more in 79.03% of patients. We also observed that 62.9% of patients had high-stage disease (III–IV), with stage IV accounting for about half of these cases (51.61%). Furthermore, 85.48% of patients had extranodal involvement and 46.77% had a moderate/high IPI risk stratification score. Specifically, the non-GCB subgroup was more prevalent, accounting for 66.13% of cases. These clinical features are consistent with what has been previously reported in the literature.[6] One study discovered that high expression of both MYC and BCL2 led to a significant decrease in the activity of genes responsible for the production and remodeling of the extracellular matrix. This is noteworthy because these genes play a crucial role in cellular structure and attachment. At the same time, another study observed an increase in the activity of genes that promote cell growth and division, fostering a more invasive phenotype in this patient subset.[8]

In terms of patient outcomes, our univariate analysis indicated that different factors, including age, Ann Arbor stage, serum lactate dehydrogenase, IPI score, and ASCT, may influence PFS. Notably, factors such as the Ann Arbor stage, IPI score, and ASCT may also be influential factors for OS. Overall, our multifactorial analysis suggested that age and ASCT were independent prognostic factors for PFS, while various clinical

factors were not associated with the likelihood of OS as an outcome.

Although there was no significant difference in PFS and OS between the GCB and non-GCB subgroups in our study, we did find that the addition of chidamide improved the prognosis of non-GCB patients. These patients are typically considered to have worse survival. For example, the 2-year PFS of non-GCB patients treated with R-CHOP alone was only 28%, with a corresponding 2-year OS of 46%.[18]

Our study also suggests that consolidation ASCT improved the PFS among treatment-responsive patients, including 17 patients with CR and one patient with PR. Nevertheless, it did not yield any improvement in OS. The use of ASCT consolidation as a first-line treatment in high-risk or intermediate-high-risk DLBCL patients is currently controversial, with previous studies showing mixed results. For example, a study by Cortelazzo et al. compared the efficacy of R-CHOP with R combined with high-dose sequential chemotherapy followed by sequential ASCT. The study found no improvement in PFS and OS with intensive chemotherapy combined with ASCT.[19] In contrast, retrospective studies have shown that in the rituximab era, first-line ASCT consolidation could prolong PFS and OS in intermediate/high-risk patients, especially in those who achieve CR.[20] Meanwhile, the SWOG-9704 study, which yielded similar findings to ours, concluded that early ASCT improved the PFS of patients with high-intermediate-risk or high-risk disease who responded to induction therapy. However, it did not impact OS after transplantation.[21] However, for patients with DHL, studies such as those by Petrich et al.[22] and Chen et al.[23] found no improvement in OS or PFS with the addition of ASCT following the achievement of a CR. Overall, limited data is available for cases with DEL. Nevertheless, the DEL subgroup in the SWOG-9704 study demonstrated a trend toward improved PFS with ASCT after the use of R-CHOP.[24] Ultimately, although our study suggests a trend toward improved PFS, it is important to note that our sample size was small. In conclusion, while ASCT may have potential benefits in specific cases, further exploration is needed to determine its overall effectiveness, including in patients with DEL.

Regarding adverse reactions and toxicity, only one case required a change in treatment regimen due to a severe rash, and there were no deaths due to TRAEs. Hematologic toxicity remained the most common adverse reaction compared to R-CHOP-21 treatment in primary DLBCL. When receiving G-CSF secondary prophylaxis, R-CHOP-21-treated patients had a 48%–60% incidence of grade 3–4 neutropenia and a 9%–11% incidence of neutrophilic fever. In our study, there was no increase in the incidence of grade 3–4 neutropenia (46.7%) and a slight increase in the incidence of neutrophilic fever (19.4%). The incidence of thrombocytopenia was similar, and although the overall incidence of anemia was increased with CR-CHOP, the incidence of grade 3–4 anemia was also comparable.[18,25] Furthermore, the most common nonhematologic toxicity compared to R-CHOP-21 was infections, with a similar incidence.[25] Additionally, increased levels of hepatic transaminases were noted, although these improved with symptomatic management. The remaining nonhematologic adverse effects, such as fatigue and gastrointestinal symptoms, were infrequent. Overall, the combination of R-CHOP based on chidamide 20 mg twice a week was generally well tolerated, aided by G-CSF secondary prophylaxis and prompt symptomatic management.

To the best of our knowledge, there are limited studies on the use of chidamide for treating newly diagnosed DLBCL. This study, however, represents the largest sample of chidamide used in combination with the conventional treatment regimen R-CHOP for first-line treatment of the double-expressor subtype of DLBCL. Notably, the study has a low loss-to-follow-up rate alongside good data completeness. Nevertheless, it is important to note that this study does have some limitations. For example, the sample size is still insufficient, although 5-year survival data was collected. Additionally, there may be some information bias due to the limited length of the follow-up period. Future studies should aim to address and improve upon these limitations.

Conclusion

DEL presents as a unique clinical entity that requires the exploration of more effective treatment regimens. This study demonstrates that for patients with newly diagnosed DLBCL DEL

subtype, the CR-CHOP treatment protocol remains highly effective over a long period. It shows promising short-term efficacy in terms of CR rate and ORR and consistently demonstrates high PFS and OS rates while maintaining a tolerable safety profile.

Declarations

Ethics approval and consent to participate

The study was approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University (No. 2024505).

Consent for publication

Not applicable.

Author contributions

Xi Chen: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author.

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Supplemental material

Supplemental material for this article is available online.

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