SCIEPublish

Article

R-CHOP *vs* R-DA-EPOCH for Double-Expressor Lymphoma: A Meta-Analysis

Rui Wu, Miao Zhang, Yue Liu, Yao Liu and Pan Zhao *

Department of Hematology, Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, China; 3221974462@qq.com (R.W.); 1098299945@qq.com (M.Z.); 2932444873@qq.com (Y.L.); 1638218335@qq.com (Y.L.)

* Corresponding author. E-mail: 66716891@qq.com (P.Z.)

Received: 15 July 2024; Accepted: 17 October 2024; Available online: 30 December 2024

ABSTRACT: Double-expressor lymphoma (DEL), a subtype of diffuse large B-cell lymphoma (DLBCL), presents a poor prognosis. The traditional R-CHOP regimen has been ineffective in treating DEL. The intensified dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-DA-EPOCH) chemotherapy regimen is considered a potential treatment strategy for DEL. This research assesses the distinction between the R-CHOP regimen and the R-DA-EPOCH regimen in treating DEL. A systematic search was conducted in the Cochrane Library, PubMed, and Embase databases, including studies through April 2023. Following literature screening, data extraction, and evaluation of study quality, a meta-analysis was executed utilizing the RevMan v5.4 software. This study included five studies in total, involving 439 patients. The findings of the meta-analysis indicated no considerable variations in the progression-free survival (HR = 1.03; 95% confidence interval, CI: 0.67–1.60; $P > 0.05$), overall survival (HR = 0.90; 95% CI: 0.60–0.34; $P > 0.05$), and objective response rate (HR = 0.97; 95% CI: 0.89–1.06; $P > 0.05$) among individuals with DEL who underwent treatment with R-CHOP and R-DA-EPOCH. This meta-analysis suggests that R-DA-EPOCH does not significantly improve the long-term prognosis of individuals with DEL compared to the R-CHOP regimen.

Keywords: Double-expressor lymphoma; R-DA-EPOCH; R-CHOP; Prognosis; Diffuse large B-cell lymphoma

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the predominant subtype of non-Hodgkin lymphoma, representing around 30%–40% of cases globally [1]. This disease exhibits heterogeneity in pathological subtypes, morphological variations, gene expression profiles, and prognoses [2]. The current first-line treatment for DLBCL involves the combination of CD20 monoclonal antibodies with the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy regimen. Although R-CHOP increased the cure rate of individuals with DLBCL from 30% to around 70% [3,4], nearly 40% of the DLBLC patients experienced relapsed or refractory DLBLC with a poor prognosis. Various factors contribute to the prognosis of individuals with DLBLC, encompassing age, international prognostic index (IPI) score, cell-of-origin subtype and specific chromosomal rearrangements or protein expressions [5,6]. Researchers recognize double-expressor lymphoma (DEL) as a subtype of DLBCL with a poor prognosis. They currently define DEL as a lymphoma that meets immunohistochemical criteria with ≥ 40% Myc-positive cells and > 50% Bcl-2-positive cells [7]. The individuals with DEL undergoing exclusive treatment with R-CHOP exhibited poor prognosis, with 5-year progression-free survival (PFS) and overall survival (OS) rates of < 40% [8,9]. Therefore, optimizing treatment strategies for DEL patients remains an ongoing challenge among researchers. The intensified dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-DA-EPOCH) chemotherapy regimen is considered a potential treatment strategy for DEL. A study by Dodero A. et al. demonstrated that individuals with DEL under 65 years of age, when treated with R-DA-EPOCH, exhibited improved PFS and OS compared to those treated with R-CHOP [10]. However, a phase III clinical trial by Bartlett et al. indicated that R-DA-EPOCH demonstrated increased toxicity compared to R-CHOP. Moreover, it failed to enhance the PFS or OS of the

DEL patients [3]. Considerable controversy surrounds the effectiveness of R-DA-EPOCH in treating DEL, emphasizing the need for further research. In response, we conducted a meta-analysis to compare the efficacy of R-CHOP and R-DA-EPOCH in treating individuals with DEL, aiming to provide a systematic evaluation of R-DA-EPOCH's effectiveness in DEL treatment.

2. Materials and Methods

2.1. Search Strategy

This systematic review conformed to the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The search for all published studies on individuals with DEL was conducted in PubMed, Cochrane Library, and Embase databases, with the search cutoff date until April 2023. Free-text terms such as "double expressor", "Myc, Bcl-2", "diffuse large B-cell lymphoma", "EPOCH", and "CHOP" were employed.

2.2. Study Selection

The inclusion criteria were defined based on: (1) study design, specifically focusing on the comparative effectiveness of R-CHOP and R-DA-EPOCH in individuals with DEL; (2) reported outcomes, including rates of CR and PR or ORR, and hazard ratios (HR) for OS or PFS. The exclusion criteria comprised: (1) article types, excluding reviews, case reports, conference abstracts, and systematic reviews; (2) participants with a subgroup size of fewer than 10 individuals; (3) a Newcastle-Ottawa Scale (NOS) score below 4 points.

2.3. Data Extraction

Two independent reviewers conducted data extraction and entry in a double-blind manner. The extracted information included the name of the first author, sample sizes of the experimental and control groups, publication year, gender and age of participants, intervention protocols, relevant outcome indicators, and other relevant data.

2.4. Statistical Analysis

Statistical analysis was performed using RevMan v5.4 software. We represented binary variables as risk ratios (RR) with their corresponding 95% confidence intervals (CI) while presenting time-related endpoints (PFS and OS) as hazard ratios (HR) with their 95% CI. Both the χ^2 test and the I^2 test were employed to evaluate heterogeneity among the studies. A fixed-effects (FE) model was applied when heterogeneity among studies was not statistically significant ($P > 0.1$ and $I^2 < 50\%$). We employed a random-effects model when detecting significant heterogeneity among the studies, excluding cases with clear clinical heterogeneity ($P \leq 0.1$ and $I^2 \geq 50\%$). Furthermore, subgroup or sensitivity analyses were conducted in cases of significant clinical heterogeneity. All hypothesis tests were performed using two-sided tests at a 5% significance level.

3. Results

3.1. Literature Search

A total of 1364 potentially relevant articles were initially identified. Of these, 267 duplicates and 1044 irrelevant articles were removed following the deduplication process, abstract screening, and full-text review. Of the remaining 53 articles, 45 had unclear outcomes, and 3 conference abstracts were excluded as well. Ultimately, the meta-analysis of this study included 5 studies (Figure 1) [3,10–13], comprising a total of 439 patients.

3.2. Study Characteristics

Among them, 218 patients underwent the R-CHOP regimen, while 221 received the R-DA-EPOCH regimen as their first-line treatment for DEL. The fundamental attributes of the incorporated studies are outlined in Table 1.

3.3. Quality Assessment

Out of the 5 studies included, 4 were retrospective in nature, and their quality was evaluated utilizing the NOS. The outcomes of the quality assessment are delineated in Table 2.

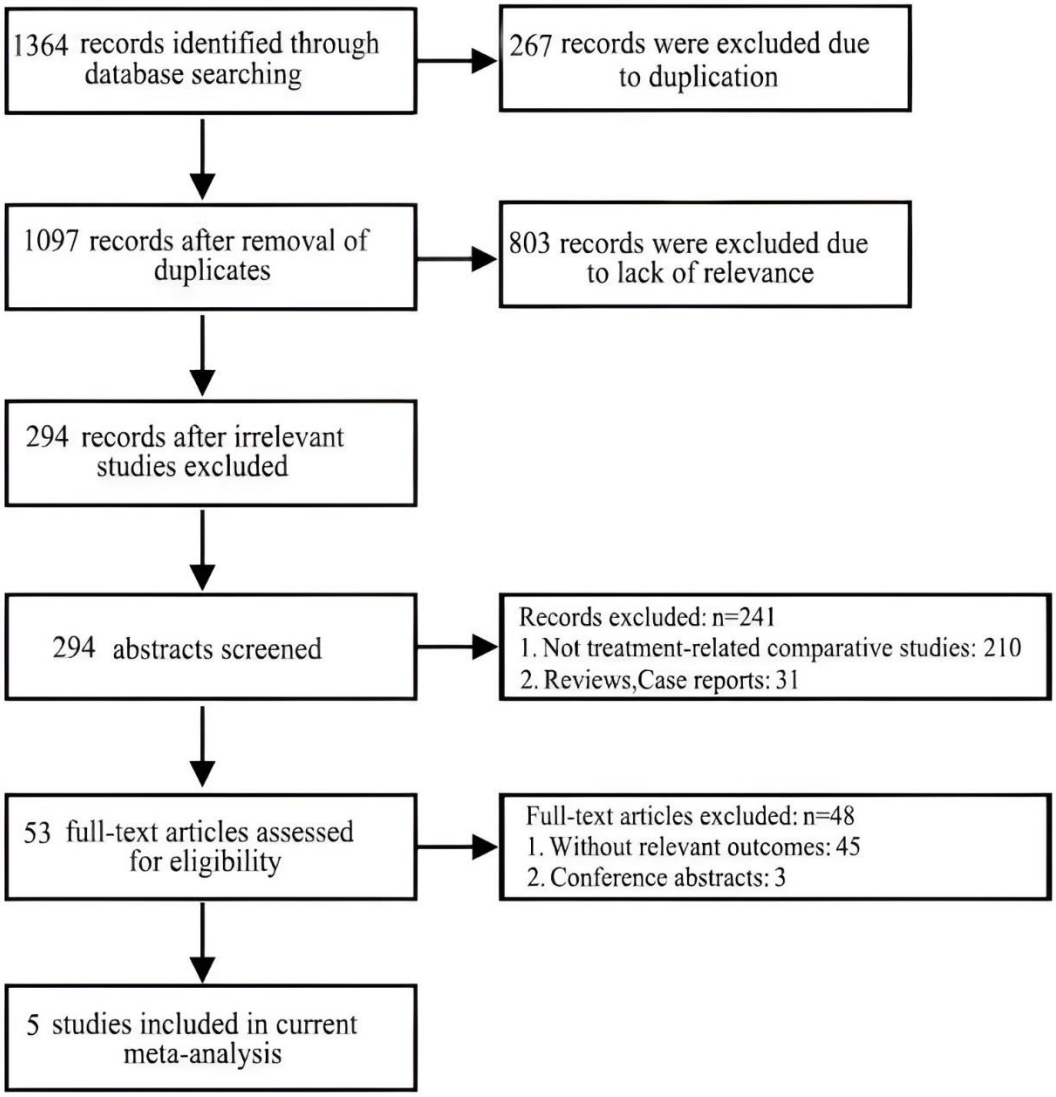

Figure 1. Flow chart of the study selection.

Table 1. Study attributes.

Year	First author	Design	Group	Median age (Y)	Male (%)	Group C (n)	Median age (Y)	Male (%)
2021	Christopher	Retrospective	39	66	57	46	66	50
2022	Othman	Retrospective	94	UN	49.2	61	UN	59.6
2019	Bartlett	RCT	20	UN	UN	22	UN	UN
2017	Pedersen	Retrospective	17	UN	UN	26	UN	UN
2019	Dodero	Retrospective	51	58	63	63	65	60

Group C: the patients of individuals undergoing R-CHOP treatment; Group E: the patients of individuals undergoing R-DA-EPOCH treatment; UN: unable to access original data; RCT: randomized controlled trial.

Table 2. Newcastle-Ottawa Scale.

Study	Year	Selection	Comparability	Exposure	Quality scores
Othman	2022	★★★	★	★★	★★★★★★
Christopher	2021	★★★★	★	★★	★★★★★★★
Pedersen	2017	★★★	★	★★★	★★★★★★★
Dodero	2019	★★	★	★★★	★★★★★★

A single study in this analysis was a randomized controlled trial, and its quality assessment was carried out utilizing the risk of bias assessment tool recommended by the Cochrane Handbook for Systematic Reviews (v5.4.1). This tool evaluated multiple domains, encompassing random sequence generation, blinding of implementers and participants, allocation concealment, completeness of outcome data, selective reporting of study results, and other sources of bias. The assessment for each domain resulted in ratings of "high risk of bias", "low risk of bias", or "unclear risk of bias" (Figure 2).

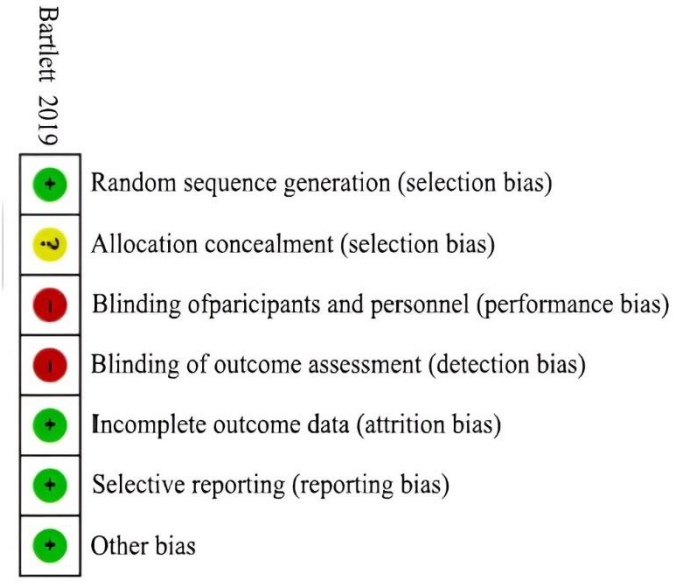

Figure 2. Risk of bias in selected study.

3.4. The Result of ORR

Three studies provided data on the ORR. Heterogeneity analysis revealed no notable heterogeneity among these studies ($I^2 = 0\%$ and $P = 0.54$). Therefore, an FE model was utilized for their meta-analysis. The findings revealed that R-DA-EPOCH did not result in a significant improvement in the ORR of the individuals with DEL relative to R-CHOP (Figure 3).

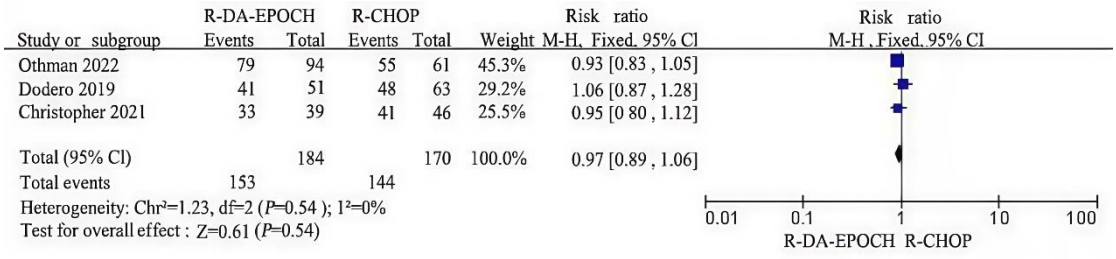

Figure 3. Forest plot of the risk ratio of ORR in individuals with DEL who underwent treatment with R-CHOP *vs* R-DA-EPOCH alone**.** M-H: Mantel-Haenszel; CI: confidence interval; df: degrees of freedom.

3.5. The Result of PFS

Four studies provided HR values for PFS. Heterogeneity analysis of these studies revealed no significant heterogeneity ($I^2 = 0\%$ and $P = 0.59$), leading to applying an FE model for the meta-analysis. The findings revealed that compared to R-CHOP, the use of R-DA-EPOCH did not result in a notable improvement in the PFS of individuals with DEL ($z = 0.14$, $P = 0.89$) (Figure 4).

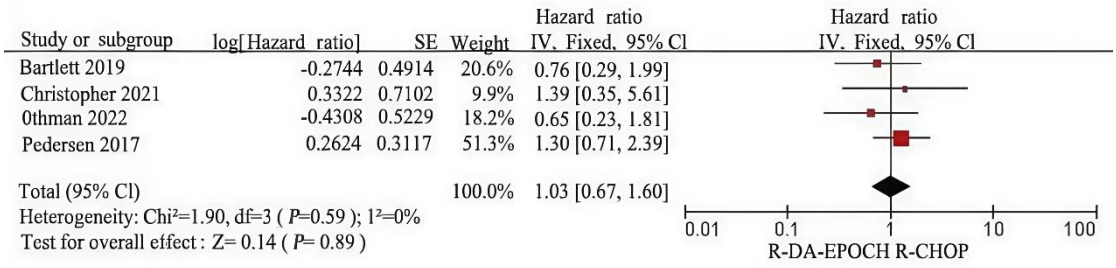

Figure 4. Forest plot of the hazard ratio of PFS in individuals with DEL who underwent treatment with R-CHOP *vs* R-DA-EPOCH. SE: standard error; CI: confidence interval; df: degrees of freedom.

3.6. The Result of OS

Three studies provided HR values for OS. Heterogeneity analysis revealed no notable heterogeneity among these studies ($I^2 = 0\%$ and $P = 0.84$). Therefore, an FE model was utilized for their meta-analysis. The findings showed that R-DA-EPOCH did not result in a significant improvement in the OS of DEL patients compared to R-CHOP (z = 0.52, $P = 0.60$) (Figure 5).

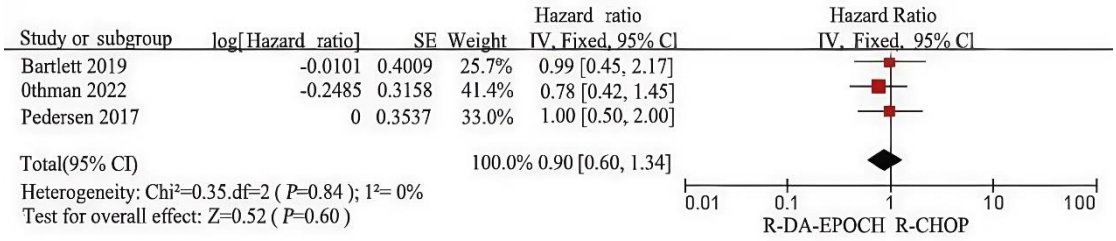

Figure 5. Forest plot of the hazard ratio of OS in individuals with DEL who underwent treatment with R-CHOP *vs* R-DA-EPOCH. SE: standard error; CI: confidence interval; df: degrees of freedom.

3.7. Publication Bias

As an observational study, meta-analysis is vulnerable to bias at different stages. One common issue in meta-analyses is publication bias, which can be evaluated using a funnel plot. In this study, a funnel plot was created by plotting the HR values of each study on the horizontal axis and the reciprocal of the HR values on the vertical axis. The funnel plot exhibited a generally symmetrical pattern, suggesting minimal publication bias (Figure 6).

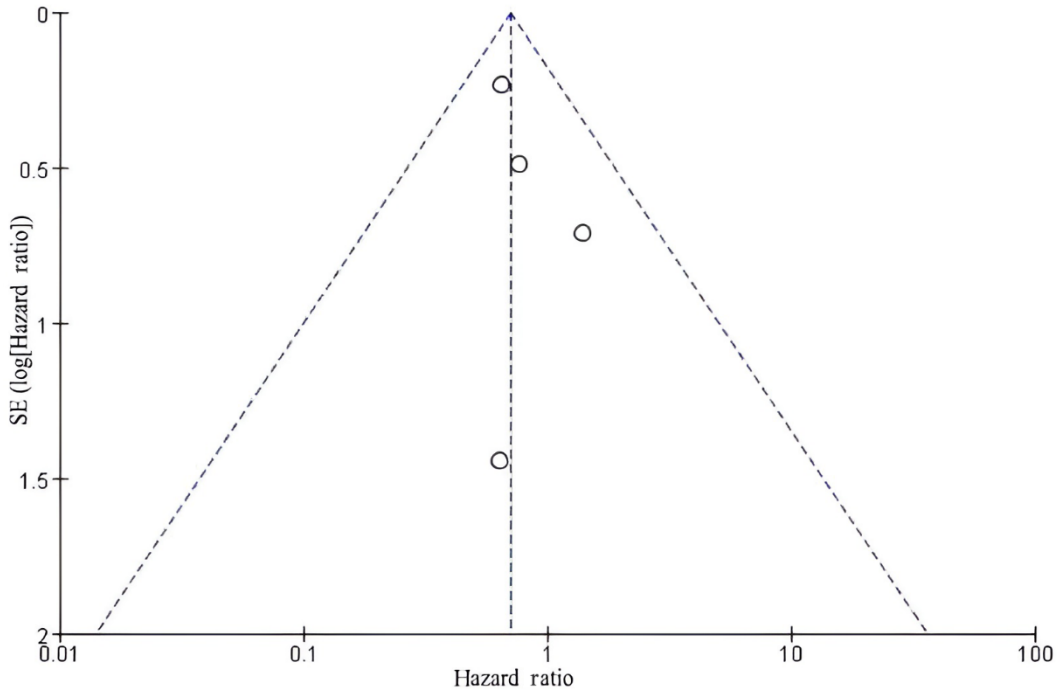

Figure 6. The funnel plot was drawn to test for publication bias. SE: standard error.

4. Discussion

The outcomes of this meta-analysis indicate no significant improvement in PFS and OS for individuals with DEL who underwent treatment with R-DA-EPOCH compared to those treated with R-CHOP. These outcomes aligned with the observations made by Bartlett et al. Conversely, Dodero A et al. observed that among DEL patients under the age of 65, individuals subjected to treatment with R-DA-EPOCH showed improved PFS (HR = 82% *vs* HR= 43%, P = 0.020) and OS (HR = 90% *vs* HR = 62%, P = 0.042) relative to those treated with R-CHOP [10]. Similarly, Othman et al. demonstrated that compared to R-CHOP, R-DA-EPOCH improved the PFS among DEL patients aged < 65 years, although it did not prolong their OS [11]. The variations in these findings may be attributed to factors not accounted for in this meta-analysis or to the absence of subgroup analysis considering factors such as age. As a result, the potential benefits of R-DA-EPOCH for certain subgroups of DEL patients cannot be dismissed solely based on this meta-analysis and should be confirmed through large-scale clinical trials. In consideration of the controversial findings regarding the efficacy of R-DA-EPOCH in DEL, it is necessary to conduct further investigation into alternative treatment options for DEL.

Autologous stem cell transplantation (ASCT) following high-dose chemotherapy is a potentially curative treatment for patients with diffuse large B-cell lymphoma. However, Herrera et al. showed that DEL patients who underwent autologous hematopoietic stem cell transplantation did not benefit compared to non-DEL patients. The 4-year OS rates were 56% and 67%, respectively (P = 0.10) [14]. The patients with DEL had poor prognosis after high-dose chemotherapy combined with ASCT, and the prognosis of DEL after allogeneic hematopoietic cell transplantation (allo-HSCT) was also not good. Kawashima et al. found that due to early disease progression, the 2-year PFS for DEL patients was only 27% [15], suggesting that neither ASCT nor allo-HSCT is a good choice for patients with DEL. Therefore, developing more precise and effective treatment strategies for DEL patients remains a significant challenge.

In a small-sample phase I clinical trial, the combination of lenalidomide with R-DA-EPOCH emerged as a potentially safe and feasible treatment option for DEL [16]. The study reported sustained and complete metabolic responses in all 10 patients within the DEL cohort, with 2-year OS and PFS rates both reaching 87% after a median follow-up period of 24 months. Furthermore, several clinical studies found that combining Bcl-2 inhibitor venetoclax and R-CHOP can improve the prognosis of DEL patients [17,18]. Zelenetz et al. demonstrated that the combination of venetoclax and R-CHOP achieved a complete response rate of 87.5% in DEL patients [17]. The phase 2 clinical trial expanded the study's sample size and demonstrated that the combination of venetoclax and R-CHOP resulted in 2-year PFS and OS rates of 72.3% and 79%, respectively, in DEL patients [18]. Furthermore, certain *in vitro* experiments showed synergistic activity between rituximab and histone deacetylase inhibitors (anti-lymphoma drugs) [19]. A phase II clinical trial revealed that combining chidamide and R-CHOP led to complete remission in all 12 DEL phenotype patients, with 2-year PFS and OS rates reaching 83% and 92%, respectively [20]. The overexpression of Myc and Bcl-2 may be associated with the activation of the B-cell receptor (BCR) and nuclear factor-kappa B signaling pathways, indicating that the BCR signaling pathway is overactive in DEL. Therefore, interventions targeting these pathways with BCR inhibitors may hold promise for improving the prognosis of DEL patients [21]. A phase III clinical trial showed that the combination of ibrutinib (oral Bruton's tyrosine kinase inhibitor) and R-CHOP (n = 123) showed improved event-free survival (HR = 0.646, P = 0.0403) and OS (HR = 0.682, P = 0.1574) compared to the combination of placebo and R-CHOP (n = 111) in individuals with DEL [22]. Moreover, CD19-targeted chimeric antigen receptor T-cell (CAR-T) therapy offers a promising approach for treating refractory DLBCL. A single-arm, multicenter, phase I–II ZUMA-1 trial showed that the CAR-T therapy elicited an objective response in 30 out of 33 DEL patients (91%), with 23 patients (70%) achieving complete remission [23]. A phase II clinical study conducted by Westin et al. reported that ibrutinib, lenalidomide, combined with R-CHOP treated initial DLBCL patients, whose PFS and OS were 91.3% and 96.6%, respectively, indicating that this regimen had good efficacy and safety for newly diagnosed DLBCL [24]. However, further clinical studies with large sample sizes and long-term follow-up are still needed to confirm the same benefit in patients with DEL.

The limitation of this study was that some raw key data could not be obtained, and univariate analysis of age, IPI score, and stage was not performed in this study.

Although some studies suggest that younger DEL patients are more likely to experience longer progression-free survival with R-DA-EPOCH, this question could not be addressed as no subgroup analysis was performed in this study. Another limitation was that the original studies cited in this study were mostly retrospective studies, we expect a large prospective trial to provide a definitive result.

5. Conclusions

This meta-analysis study suggests that in DEL patients, the R-DA-EPOCH regimen can not improve the ORR, PFS, and OS rates compared with the R-CHOP regimen. In DEL patients, the potential therapeutic benefits shown by the new targeted agents in combination with R-CHOP or R-DA-EPOCH regimens suggest that combination therapy may be a more viable treatment.

Author Contributions

Conceived the ideas and designed this project, P.Z.; Concept, literature review, and writing, R.W.; Design, analysis and interpretation, and literature review, M.Z.; Data collection and drafting, Y.L. (Yao Liu); Interpretation of data and critical revision, Y.L. (Yue Liu).

Ethics Statement

Not applicable.

Informed Consent Statement

Not applicable.

Funding

This work was supported by the Natural Science Foundation of Sichuan (2022NSFSC1416 to PZ).

Declaration of Competing Interest

The authors declared no conflict of interests.

References

1. Lu T, Zhang J, Xu-Monette ZY, Young KH. The progress of novel strategies on immune-based therapy in relapsed or refractory diffuse large B-cell lymphoma. *J. Exp. Hematol. Oncol*. **2023**, *12*, 72.
2. Wright GW, Huang DW, Phelan JD, Coulibaly ZA, Roulland S, Young RM, et al. A Probabilistic classification tool for genetic subtypes of diffuse large B cell lymphoma with therapeutic implications. *J. Cancer Cell* **2020**, *37*, 551–568.
3. Bartlett NL, Wilson WH, Jung SH, Hsi ED, Maurer MJ, Pederson LD, et al. Dose-adjusted EPOCH-R compared with R-CHOP as frontline therapy for diffuse large B-cell lymphoma: clinical outcomes of the phase III intergroup trial alliance/CALGB 50303. *J Clin Oncol*. **2019**, *37*, 1790–1799.
4. Fuji S, Kida S, Nakata K, Morishima T, Miyashiro I, Ishikawa J. Analysis of real-world data in patients with relapsed/refractory diffuse large B cell lymphoma who received salvage chemotherapy in the rituximab era. *Ann. Hematol.* **2021**, *100*, 2253–2260.
5. Ruppert AS, Dixon JG, Salles G, Wall A, Cunningham D, Poeschel V, et al. International prognostic indices in diffuse large B-cell lymphoma: a comparison of IPI, R-IPI, and NCCN-IPI. *Blood* **2020**, *135*, 2041–2048.
6. Sehn L H, Salles G. Diffuse large B-cell lymphoma. *Engl. J. Med.* **2021**, *384*, 842–858.
7. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the world health organization classification of lymphoid neoplasms. *Blood* **2016**, *127*, 2375–2390.
8. Johnson NA, Slack GW, Savage KJ, Connors JM, Ben-Neriah S, Rogic S, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J. Clin. Oncol.* **2012**, *30*, 3452–3459.
9. Hu S, Xu-Monette ZY, Tzankov A, Green T, Wu L, Balasubramanyam A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from the international DLBCL rituximab-CHOP consortium program. *Blood* **2013**, *121*, 4021–4031.
10. Dodero A, Guidetti A, Tucci A, Barretta F, Novo M, Devizzi L, et al. Dose-adjusted EPOCH plus rituximab improves the clinical outcome of young patients affected by double expressor diffuse large B-cell lymphoma. *Leukemia* **2019**, *33*, 1047–1051.
11. Othman T, Penaloza J, Zhang S, Daniel CE, Gaut D, Oliai C, et al. R-CHOP Vs DA-EPOCH-R for double-expressor lymphoma: a university of california hematologic malignancies consortium retrospective analysis. *Clin. Lymphoma. Myeloma Leuk*. **2022**, *22*, e947–e957.

12. Pedersen M, Gang AO, Brown P, Pedersen M, Knudsen H, Nielsen SL, et al. Real world data on young patients with high-risk diffuse large B-cell lymphoma treated with R-CHOP or R-CHOEP - MYC, BCL2 and BCL6 as prognostic biomarkers. *PLoS ONE* **2017**, *12*, e0186983.
13. D'Angelo CR, Hanel W, Chen Y, Yu M, Yang D, Guo L, et al. Impact of initial chemotherapy regimen on outcomes for patients with double-expressor lymphoma: a multi-center analysis. *Hematol. Oncol.* **2021**, *39*, 473–482.
14. Herrera AF, Mei M, Low L, Kim HT, Griffin GK, Song JY, et al. Relapsed or refractory double-expressor and double-hit lymphomas have inferior progression-free survival after autologous stem-cell transplantation. *J. Clin. Oncol.* **2017**, *35*, 24–31.
15. Kawashima I, Inamoto Y, Maeshima AM, Nomoto J, Tajima K, Honda T, et al. Double-expressor lymphoma is associated with poor outcomes after allogeneic hematopoietic cell transplantation. *Biol. Blood Marrow Transplant.* **2018**, *24*, 294–300.
16. Godfrey JK, Nabhan C, Karrison T, Kline JP, Cohen KS, Bishop MR, et al. Phase 1 study of lenalidomide plus dose-adjusted EPOCH-R in patients with aggressive B-cell lymphomas with deregulated MYC and BCL2. *Cancer* **2019**, *125*, 1830–1836.
17. Zelenetz AD, Salles G, Mason KD, Casulo C, Le Gouill S, Sehn LH, et al. Venetoclax plus R- or G-CHOP in non-Hodgkin lymphoma: results from the CAVALLI phase 1b trial. *Blood* **2019**, *133*, 1964–1976.
18. Morschhauser F, Feugier P, Flinn IW, Gasiorowski R, Greil R, Illés Á, et al. A phase 2 study of venetoclax plus R-CHOP as first-line treatment for patients with diffuse large B-cell lymphoma. *Blood 2021*, *137*, 600–609.
19. Chen X, Wang H, Sun X, Su L, Liu F, Zhao K, et al. Safety of chidamide plus rituximab in elderly patients with relapsed or refractory B-cell lymphoma in China: a multicenter, single-arm, phase II study. *Ann. Transl. Med.* **2021**, *9*, 1769.
20. Zhang MC, Fang Y, Wang L, Cheng S, Fu D, He Y, et al. Clinical efficacy and molecular biomarkers in a phase II study of tucidinostat plus R-CHOP in elderly patients with newly diagnosed diffuse large B-cell lymphoma. *Clin. Epigen.* **2020**, *12*, 160.
21. Landsburg DJ, Hughes ME, Koike A, Bond D, Maddocks KJ, Guo L, et al. Outcomes of patients with relapsed/refractory double-expressor B-cell lymphoma treated with ibrutinib monotherapy. *Blood Adv*. **2019**, *3*, 132–135.
22. Johnson PWM, Balasubramanian S, Hodkinson B, Shreeve SM, Sun S, Srinivasan S, et al. Clinical impact of ibrutinib plus R-CHOP in untreated DLBCL coexpressing BCL2 and MYC in the phase 3 PHOENIX trial. *Blood Adv*. **2023**, *7*, 2008–2017.
23. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, 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*, 31–42.
24. Westin J, Davis RE, Feng L, Hagemeister F, Steiner R, Lee HJ, et al. Smart start: rituximab, lenalidomide, and ibrutinib in patients with newly diagnosed large B-cell lymphoma. *J. Clin. Oncol.* **2023**, *41*, 745–755.