Received: 20 June 2023 | Revised: 2 August 2023 | Accepted: 2 November 2023

DOI: 10.1002/hsr2.1716

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Prognosis and complete remission rate of diffuse large B-cell lymphoma patients in standard R-CHOP with reduction of vincristine: A retrospective study

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Funding information

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Abstract

Background and Aims: The effect of stopping or reducing the dose of vincristine in diffuse large B-cell lymphoma (DLBCL) on the outcome and prognosis of the disease is still in doubt. The present study aimed to investigate and compare the prognosis and complete remission of two R-CHOP treatment regimens with and without vincristine reduction in DLBCL patients.

Methods: This retrospective study was conducted on newly diagnosed DLBCL patients during 2018–2021. The patients were over 18 years of age, had been histologically confirmed by a pathologist, and were under treatment with R-CHOP regimen. The clinical information of the subjects as well as the number of treatment courses were extracted from their medical records and then compared.

Results: Overall, 269 patients with DLBCL were included in this study, 15.99% of whom ($n = 43$) had vincristine reduction. There was no significant difference between the studied factors regarding the reduction of vincristine and the complete R-CHOP regimen ($p > 0.05$). Besides, no difference was observed in the 1-year overall survival (OS) and progression-free survival (PFS) of the patients in the two groups treated with R-CHOP regimen with and without vincristine reduction ($p > 0.05$). The complete remission rates of the patients treated with R-CHOP regimen with and without vincristine ($p > 0.05$) were not different either. The results of the Cox multivariate regression showed that reducing the dose of vincristine from the R-CHOP treatment regimen had no relationship with the 1-year OS and PFS of the DLBCL patients (hazard ratio $[HR]_{OS} = 1.59$, 95% confidence interval [CI]: 3.67–0.690, $HR_{PFS} = 1.67$, 95% CI: 0.798–3.82).

Conclusion: The results of this study showed that the reduction of vincristine from the R-CHOP regimen in the DLBCL patients was not likely to make a difference in the 1-year OS and PFS of the patients. However, further studies are needed on the issue.

KEYWORDS
DLBCL, prognosis, R-CHOP, vincristine

1 | INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is one of the most common hematological malignancies, accounting for about 31% of all lymphoid malignancies and approximately 50% of non-Hodgkin's lymphoma cases.[1] The main standard treatment of these patients is chemotherapy along with the R-CHOP regimen, which has a history of at least 2 decades.[2,3] Normally, the R-CHOP treatment regimen is used as a standard regimen (3–8 courses) in all types of limited to extensive involvement in most cases of DLBCL. The regimen includes rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone.[2–6] However, despite the extensive research conducted on DLBCL patients in recent decades, it is still difficult to identify new regimens that provide significant improvements compared to CHOP in terms of prognosis as well as progression-free survival (PFS) and overall survival (OS).[7] In addition, more than half of the DLBCL patients are over 50 years of age who not only show lower responses to the treatment but are also more exposed to toxicities related to chemotherapy regimens such as Cytopenia.[5,8–10]

On the one hand, studies have shown that maintaining a high relative dose intensity (RDI) from the R-CHOP regimen with or without Rituximab is associated with improved prognosis of free survival and OS in DLBCL patients, and on the other hand, reduced RDI is associated with a poor prognosis of the patients.[11–14] Moreover, the incidence of dose-limiting toxicity with each factor of the R-CHOP regimen is associated with final outcomes.[3,4,13] Vincristine is included in this regimen and has neurotoxic and ocular side effects, among which limb paresthesia is sometimes irreversible and leads to discontinuation of the drug administration.[15,16]

Although the effectiveness of reducing or omitting vincristine from the R-CHOP regimen in DLBCL patients has not been well known, sometimes this drug is reduced or omitted from the regimen due to its side effects in the patients, such as the occurrence of peripheral neuropathy and ileus.[17] However, in case of the occurrence of side effects such as peripheral neuropathy, the administration of vincristine can be stopped or its dose can be reduced. On the other hand, the effect of stopping or reducing the dose of vincristine in DLBCL patients on the outcome and prognosis of the disease is still questionable. Hence, due to the lack of sufficient evidence on the effects of omitting or reducing vincristine from the R-CHOP regimen on the OS and PFS of DLBCL patients, this study aimed to investigate and compare the effects of reducing the number of vincristine treatment courses from the R-CHOP regimen on complete remission and prognosis of DLBCL patients.

2 | MATERIALS AND METHODS

2.1 | Study design

This retrospective study was designed according to the Strengthening the Reporting of Observational Studies in Epidemiology[18] and reporting of evidence from Clinical research in the Hematology–Oncology Department of Qaem and Imam Reza hospitals in 2018–2021 after the ethics committee approval (approved with the code: IR.MUMS.MEDICAL.REC.1400.553).

2.2 | Inclusion/exclusion criteria

The subjects were the patients diagnosed with DLBCL, who referred to Qaem and Imam Reza hospitals during 2018–2021. All the DLBCL patients over the age of 18 who were histologically confirmed by a pathologist and were under treatment with R-CHOP regimen were included in the study. The patients who were not being treated with R-CHOP regimen or were under treatment with other similar regimens such as CHOEP, dose-adjusted EPOCH-R, and radiation monotherapy, as well as the individuals with negative CD20 and follicular lymphoma were excluded from the study.

2.3 | Procedure

The clinical and demographic information of the subjects, including age, sex, serum lactate dehydrogenase (LDH), stage, and complete remission, were collected and recorded from their medical records. Using the patients' telephone numbers available in their files and having access to the treating doctors, the researchers followed up the subjects and the latest disease status as well as the 1-year OS and PFS (specifically by the project manager doctor) and recorded them in the study checklist.

The R-CHOP drug regimen included a combination of rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 (maximum 2.0 mg/m^2) along with prednisolone 60 mg/m^2, which was injected intravenously. Normally, the R-CHOP regimen is a 3-week cycle with or without radiation therapy, and the treatment is completed after 3–6 courses.

In previous studies, the dosage of the R-CHOP regimen components was usually reduced or omitted at any stage based on the opinions of the doctors due to the presence of concomitant illnesses and also based on the age of the patients and to reduce drug toxicity. For instance, cyclophosphamide and doxorubicin were reduced due to hematological and nonhematological toxicities, and prednisolone was reduced in case of having diabetes or infection with

hepatitis B. Normally, the dosage of the drug regimen components in patients suffering from febrile neutropenia or myelotoxicity can be reduced up to 80% in subsequent courses of treatment. In this study, the reason for reducing vincristine from the R-CHOP regimen was its unavailability and rarity in the medical centers under study (due to its nonimportation). OS is usually defined as the time from the start of medical treatment until death or the end of the follow-up period, and PFS is defined as the time between the start of treatment and the occurrence of tumor recurrence or death for any reason.[17] The number of the patients' treatment courses was extracted from their medical records, and the courses were compared not only in terms of number but also in terms of receiving or not receiving vincristine.

2.4 | Statistical methods

The descriptive statistics such as mean, standard deviation, and frequency distribution were used to describe the data. The Mann–Whitney test was also used to examine the difference in the mean values of the quantitative variables in the two groups with nonnormal distribution, and the Fisher exact test was used to compare the qualitative variables. The area under the Kaplan–Meier plot and the log-rank test were also used to examine and compare the survival functions in the two groups. Regarding the survival-based outcomes (time-to-event outcomes), the 1-year OS and the 1-year PFS were used. Moreover, the researchers used the Cox proportional hazard model to investigate the factors affecting the prognosis of the disease. The statistical analysis was done using the Stata 12 software (Corp), and the significance level in this study was considered <0.05. All significance levels reported were two-domain.

3 | RESULTS

A total of 269 patients with DLBCL were included in this study, 15.99% of whom ($n = 43$) had a reduction in vincristine (37.21%, 30.23%, and 32.56% had a reduction in one, two, and three courses of vincristine from the R-CHOP regimen, respectively) (Table 1). The results showed that there was no significant difference between the age distributions of the people under R-CHOP regimen with and without vincristine ($p > 0.05$). The death rate was also higher among the subjects under the R-CHOP regimen with the omission or reduction of vincristine ($p < 0.01$). Considering other factors, there was no significant difference between the reduction or omission of vincristine in terms of stage, LDH, Ki67, international prognostic index (IPI), and complete remission ($p > 0.05$) (Table 2). The results of the 1-year survival analysis showed that there was no significant difference between the OS and PFS of the two groups treated with R-CHOP regimen with and without vincristine reduction ($p > 0.05$) (Figure 1). Regarding the number of reduced courses, the results indicated that there was no significant difference between the survival rates of the patients in terms of the reduced number of vincristine courses ($p > 0.05$). On the other hand, no significant difference was found between the complete remission and relapse rates of the patients treated with R-CHOP regimen with and without vincristine ($p > 0.05$) (Figure 2).

TABLE 1 Frequency of vincristine treatment course reductions in DLBCL patients.

Course	*N* (%)
1. Course reduction	16 (37.21%)
2. Course reduction	13 (30.23%)
3. Course reduction	14 (32.56%)

Abbreviation: DLBCL, diffuse large B-cell lymphoma.

TABLE 2 Clinical and demographic information of the subjects in two groups: with vincristine and with reduction or omission of vincristine.

Variables	With vincristine reduction ($n = 43$)	Without vincristine reduction ($n = 226$)	*p*-Value
Age (year)			
<60	26 (60.46%)	147 (65.04%)	0.604
≥60	17 (39.54%)	79 (34.96%)	
Gender			
Male	18 (41.86%)	90 (39.82%)	0.866
Female	25 (58.14%)	136 (60.18%)	
Stage			
1–2	21 (55.26%)	120 (56.07%)	0.926
3–4	17 (44.74%)	94 (43.93%)	
LDH	440.22 ± 45.03	508.91 ± 22.05	0.234
Ki67	62.83 ± 3.13	66.78 ± 1.29	0.227
IPI			
0–2	19 (44.18%)	121 (53.54%)	0.318
3–5	24 (55.82%)	105 (46.46%)	
Death	20 (46.51%)	45 (19.91%)	0.001
Complete remission	19 (44.18%)	94 (41.59%)	0.866

Abbreviations: IPI, international prognostic index; LDH, lactate dehydrogenase.

The results of the Cox regression showed no significant relationship between the age and the 1-year OS of the DLBCL patients under treatment with the R-CHOP regimen (hazard ratio [HR] = 1.13, 95% confidence interval [CI]: 0.861–2.06). No significant correlation was observed between the OS and 1-year PFS of other studied factors, either ($p > 0.05$). According to the results, there was no significant relationship between the reduction of vincristine from the R-CHOP treatment regimen and the 1-year OS and PFS of the DLBCL patients ($HR_{OS} = 1.59$, 95% CI: 0.690–3.67, $HR_{PFS} = 1.67$, 95% CI: 0.798–3.82) (Table 3).

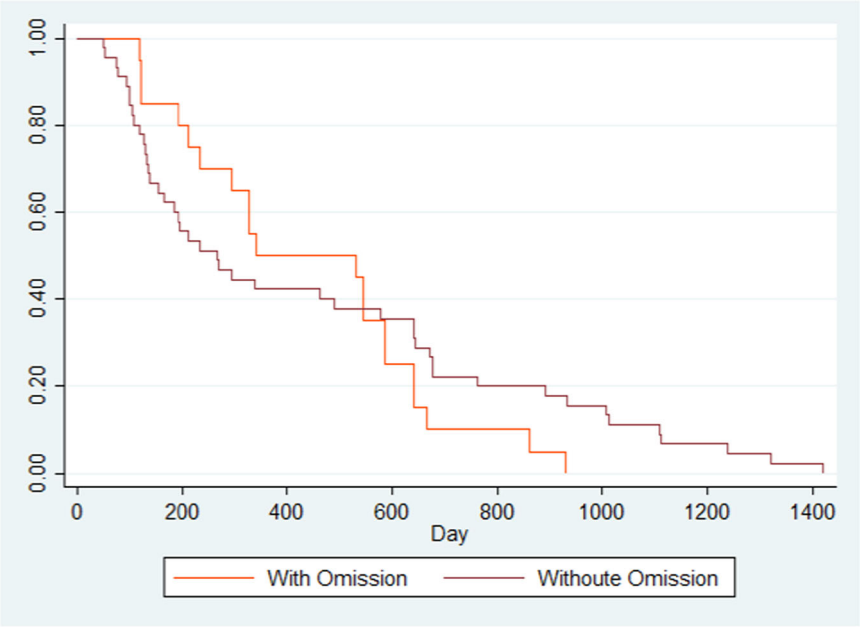

FIGURE 1 Kaplan–Meier plot comparing the survival rates of DLBCL patients under R-CHOP regimen with and without vincristine. DLBCL, diffuse large B-cell lymphoma.

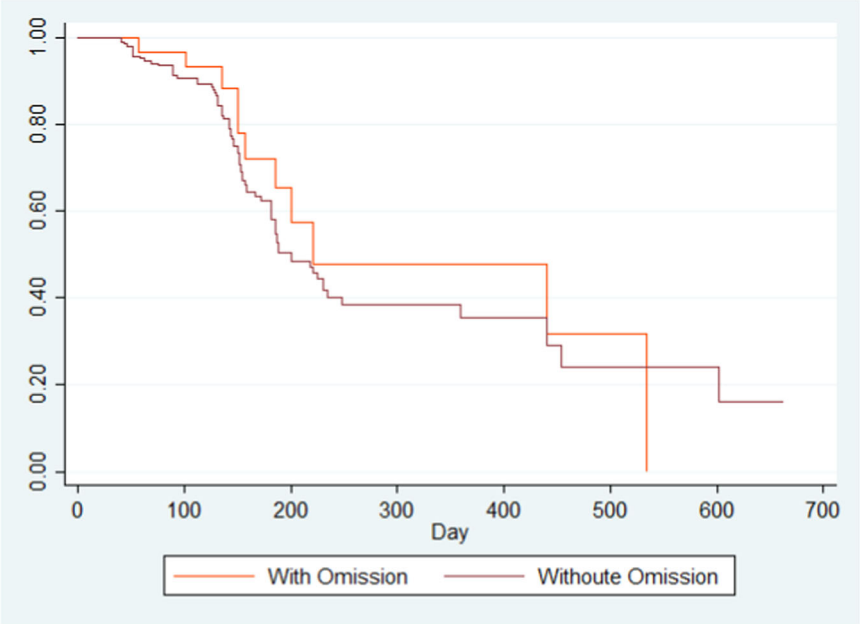

FIGURE 2 Kaplan–Meier plot comparing the complete remission rates of DLBCL patients under R-CHOP regimen with and without vincristine. DLBCL, diffuse large B-cell lymphoma.

4 | DISCUSSION

The results of this study, which examined the effect of reducing some vincristine treatment courses from the R-CHOP regimen on the prognosis and survival of DLBCL patients, showed well that reducing vincristine from the regimen had no significant effect on the 1-year survival and prognosis of the DLBCL patients. In some other studies, it was shown that the effect of age on reducing or omitting vincristine from the R-CHOP regimen could be due to the occurrence of high toxicity as well as the presence of comorbidities in these people.[9] However, it was different in the present study, and most cases of vincristine dose reduction in the DLBCL patients were due to the unavailability of the drug in the medical centers (as a result of drug sanctions). R-CHOP was usually suggested as a standard treatment regimen when rituximab was introduced in DLBCL patients.[3,4] Nevertheless, the effects of reducing or omitting vincristine from the R-CHOP regimen on the treatment of DLBCL patients have not been fully investigated. Normally, there is a correlation between the incidence and severity of vincristine neurotoxicity and the dose and duration of the drug taken by the patients. On the other hand, there is a significant difference between the pharmacokinetics of vincristine in the patients, but there is no clear relationship between the plasma levels of vincristine and neurotoxicity in these patients.[19,20] The results obtained in this study might probably be attributed to the relationship between neurotoxicity due to the high intracellular bioavailability of vincristine and better treatment responses.[9,14]

TABLE 3 Multivariable Cox regression analysis of 1-year OS and PFS of DLBCL patients.

	OS		PFS	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age ≥ 60	1.13 (0.861–2.06)	0.267	–	–
Gender (male)	0.977 (0.581–1.64)	0.930	0.861 (0.638–1.94)	0.631
LDH	1.044 (0.980–1.12)	0.385	1.19 (0.879–1.73)	0.592
Stage (III–IV)	1.32 (0.442–1.75)	0.720	1.19 (0.610–1.98)	0.764
IPI (3-5)	1.61 (0.797–3.27)	0.183	1.87 (0.641–4.06)	0.261
Vincristine reduction	1.59 (0.690–3.67)	0.183	1.67 (0.798–3.82)	0.275
Ki67	0.995 (0.981–1.91)	0.554	0.953 (0.871–2.38)	0.684

Abbreviations: CI, conidence interval; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; IPI; international prognostic index; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

The potential effects of omitting or reducing vincristine from the drug regimen on the prognosis of the DLBCL patients were also investigated. Mörth et al.[9] examined the effect of vincristine omission on the therapeutic outcome of 541 patients with DLBCL, and stated that vincristine omission occurred in about 17.6% of the patients, but it did not have any significant effects on their PFS and OS. This is in line with the results of the present study in which the occurrence of side effects such as neurotoxicity could lead to the omission of vincristine from the R-CHOP treatment regimen. However, there was no significant difference in other investigated factors such as age, LDH, IPI score, stage, and Ki67 of the subjects with and without vincristine reduction, which is consistent with the results of other studies.[9,17] In the present research, vincristine reduction from the R-CHOP regimen occurred in 15.99% of the subjects. Gutiérrez et al.[13] reviewed and compared R-CHOP14 and R-CHOP21 regimens, and suggested that the two regimens would not be different in terms of the survival functions and their prognostic roles if RDI was not reduced. In their study, Marshall et al.[17] investigated the effects of omitting or reducing vincristine from the R-CHOP treatment regimen in the treatment of DLBCL patients and showed that the 4-year OS rates of the patients with and without vincristine and with the RDI < 80% were 70% and 82%, respectively. They were also 70% and 82% ($p < 0.05$) in the patients with RDI < 50%, and 53% and 82% in the patients with RDI < 25%, respectively. In general, Marshall et al.[17] showed that omission or excessive reduction of vincristine might lead to the loss of R-CHOP efficacy in the DLBCL patients, which is contrary to the results of the present study. Hirakawa et al.[12] clearly indicated that RDI < 70% was a prognostic factor associated with worse OS and PFS of the patients. In their research, Zhang et al.[21] indicated that the adjusted doses in EPOCH-R and R-CHOP treatment regimens did not have a difference in the OS rates of the DLBCL patients, which is in line with the results of this study. It was well shown in the present study that reducing the dose of vincristine from the R-CHOP had no potential effect on the 1-year survival rate and prognosis of the DLBCL patients. However, this research had several limitations as follows. It was conducted as a retrospective cohort study, and the quality of data recording in the time trend was unclear for the researchers. In addition, the RDI of the patients in this study was not calculated due to the lack of sufficient information. On the other hand, due to the limitations of the sample size, the number of cases with reduction or omission of vincristine from the R-CHOP regimen was low, and the generalization of the results should be done with caution. On the other hand, further studies with larger sample sizes and more studies with clinical trial designs in this field are needed to increase the evidence of the ineffectiveness of reducing the number of vincristine courses on the survival of DLBCL patients.

5 | CONCLUSION

The results of this study showed that reducing the number of Vincristine treatment courses from the R-CHOP regimen in the DLBCL patients did not make a difference in the 1-year OS and PFS of the patients. In general, conducting further studies and increasing the evidence in this field will help to act more confidently when reducing or omitting vincristine in the occurrence of neurotoxicity in DLBCL patients.

AUTHOR CONTRIBUTIONS

Fatemeh Riasi: Data curation; investigation; resources; validation; writing—original draft. **Sajjad Ataei Azimi**: Conceptualization; methodology; project administration; supervision. **Abolghasem Allahyari**: Methodology; validation; visualization. **Mohammad Moeini Nodeh**: Data curation; funding acquisition; software; supervision. **Mohammad T. Shakeri**: Data curation; formal analysis; methodology; validation. **Mostafa Kamandi**: Conceptualization; methodology; project administration.

ACKNOWLEDGMENTS

This study was supported by Mashhad University of Medical Sciences.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

TRANSPARENCY STATEMENT

The lead author Mostafa Kamandi affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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How to cite this article: Riasi F, Ataei Azimi S, Allahyari A, Moeini Nodeh M, Shakeri MT, Kamandi M. Prognosis and complete remission rate of diffuse large B-cell lymphoma patients in standard R-CHOP with reduction of vincristine: a retrospective study *Health Sci Rep*. 2023;6:e1716. doi:10.1002/hsr2.1716