A multicenter retrospective study of 239 patients aged over 70 years with diffuse large B-cell lymphoma in China

Chunli Yang

West China Hospital of Sichuan University

Qiaoer Li

West China Hospital of Sichuan University

Li Li

Sichuan Cancer Hospital

Ke Xie

Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital

Yakun Zhang

Affiliated Hospital of North Sichuan Medical College

Yunwei Han

Affiliated Hospital of Southwest Medical University

Liqun Zou (✉ hxlcyxy@163.com)

West China Hospital of Sichuan University

Research Article

Keywords:

Posted Date: February 7th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1257590/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma subtype worldwide and frequently occurs in the elderly population. However, there was a lack of large series of data regarding the clinical profiles of over 70 years in DLBCL patients in China. We aim to summarize this population's clinical features and survival outcomes in the real world.

Methods

The multicenter retrospective study was conducted in Western China from Jan 2012 to July 2020 to investigate clinical features and survival outcomes of 239 DLBCL patients over 70 years. All patients underwent pre-treatment evaluations, treatment, and follow-up at local hospitals. The primary endpoints of this study were progression-free survival (PFS) rate and overall survival (OS) rate at two years. The second endpoints included median PFS and OS, 5-year PFS and OS rates, and adverse events during treatment.

Results

With a median follow-up of 50 months (range, 1-102), the 2-year PFS and OS rates were 53.0% (95% CI: 46.5-59.5) and 65.5% (95% CI: 59.4-71.2). The median PFS and OS were 42.1 months and 96.4 months, and the 5-year PFS and OS rates were 44.7% (95% CI: 38.0-51.4) and 56.1% (95% CI: 49.4-62.8). Hematological toxicities were the most common adverse effects in this study, accounting for 90.4%, and leukopenia was the most frequently observed $\geq$ grade 3 events. Moreover, we observed that no rituximab-containing treatment and chemotherapy cycles < 6 were significantly associated with inferior survival. Furthermore, in the younger than 80 years group, reduced chemotherapy dose was associated with remarked shorter OS; the 2-y OS rate was 74.4% (95% CI: 67.0-81.8) in full dose group in comparison with 67.1% (95% CI: 51.8-82.4) in decreased dose group, p 0.044.

Conclusions

Our study indicated that rituximab, enough treatment cycles, full chemotherapy dose should be administered for elderly DLBCL patients under the balance of benefit and risk.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma subtype worldwide, accounting for 30 ~ 40% of non-Hodgkin lymphoma^[1]. From the SEER (Surveillance, Epidemiology, and End Results Program) database, the incidence of DLBCL increases with age; the median diagnosis age was 66 years^[2]. Compared to DLBCL patients younger than 60-70 years, older patients had a worse prognosis^[3-5]. Moreover, most clinical trials excluded these patients, leading the optimal treatment options and the survival outcome in the real-world remain to be elucidated, especially for over 70 years.

R-CHOP is the standard regimen for the first-line DLBCL treatment^[6, 7], reaching a 60% cure rate for the entire cohort^[8]. Whereas most elderly patients had poor physical state and were frequently accompanied by other diseases, which limited the usage of standard dose of the regimen and further had a worse impact on the survival. Thus, dose reduce regimens or no-anthracycline-containing treatment were explored in clinical trials, such as R-miniCHOP, R-GemOx, R2^[9–11], which resulted in a balance of efficacy and tolerance in selected elderly DLBCL patients. In the United States, the 5-year survival rate was 78.4% in the DLBCL population of those younger than 55 years, while 54.3% was for people older than 65 years^[2]. In China, it reported that 5-year OS rate 51.9% for DLBCL patients aged over 60 years between 2006 to 2012 in Beijing of 349 cases, and 42.8% for aged over 70 years of 145 patients^[12]. To date, there has been a limited number of studies regarding the clinical profiles of aged over 70 years in DLBCL patients. Furthermore, as the anti-CD20 antibody was widely applied in clinical practice in Western China, and better administration of treatment related adverse effects in recent years than ever, indicating that the survival outcome of Chinese elderly DLBCL needs to be investigated.

In this study, we collected 239 DLBCL patients aged over 70 years from five university hospitals in Western China to summarize the clinical features, analyze survival outcomes in the real world, and examine the factors that influenced the prognosis.

Methods

We retrospectively reviewed the record of all newly diagnosed DLBCL patients who were aged over 70 years at five hospitals located in southwest China from Jan 2012 to July 2020, including West China Hospital, Sichuan University; Sichuan Cancer Hospital & Institute, Sichuan Provincial People's Hospital; Affiliated Hospital of North Sichuan Medical College and Affiliated Hospitals of Southwest Medical University. In all cases, the pathology diagnosis was confirmed by expert hematopathologists at these five hospitals per the World Health Organization classification of hematopoietic and lymphoid tumors^[13]. Critical exclusion criteria were age less than 70, central nervous system lymphoma involvement at diagnosis.

All patients underwent pre-treatment evaluations, treatment, and follow-up at the local hospital mentioned above. Evaluations included patient demographics, blood test, serum LDH, bone marrow detection. The staging was determined per the Ann Arbor staging system, and the treatment efficacy was evaluated by the enhanced computed tomography scans (CT) or positron emission tomography scans (PET-CT). Han's algorithm was applied to divide patients into germinal center B-cell (GCB) and non-GCB subtypes. The bulky disease was defined as any mass diameter exceeding 7 cm. The investigators also reviewed the therapy options, regimens, cycles, and adverse events. Reduced dose chemotherapy in this study was explained as a decrease of 20% - 50% of standard dose.

The primary endpoints of this study were PFS rate and OS rate at two years. The second endpoints included median PFS and OS, 5-year PFS and OS rate, adverse events during treatment. The PFS was calculated from the diagnosis to disease progression, recurrence, or any cause of death, and the OS was

from the diagnosis to death for any reason or last follow-up. The study was done under regulatory requirements and approved by the Ethics Committee of West China Hospital of Sichuan University.

The statistical methods of comparing the difference between the groups were the χ^2 test. We summarized PFS and OS using the Kaplan-Meier method, compared the difference between groups on PFS and OS with the log-rank test. Univariate and multivariate analyses related to survival were through the Kaplan-Meier method, the Cox proportional hazard models and the log-rank test. All data were analyzed with SPSS 25.0 (IBM Corp., Armonk, NY), and a two-sided $p < 0.05$ was considered a statistically significant difference.

Results

Patient characteristics

We identified 316 patients newly diagnosed with DLBCL aged over 70 years from Jan 2012 to July 2020. Of these screened patients, 22 cases had other malignant tumors concurrent, and 55 patients had only pathological diagnosis were excluded; 239 patients were finally included in the analyses.

Clinical characteristics are listed in Table1. The median age at diagnosis was 75.4 years (range, 70-91), and the ratio of male to female was 1.5:1. Staged III/IV patients were accounted for 59.8%, and 27.2% for extranodal involved more than one site. There were 200 patients had subtypes via Han's algorithm, 21.8% for GCB, 61.9% for non-GCB, and 16.3% of patients remained unknown. According to the IPI score, 25.5% of cases were evaluated as a high-risk group. It was 85.8% of patients accompanied by other diseases. From the subgroups analysis data, between patients younger and older than 80 years, we observed no significant difference at baseline on clinical features.

Treatment and response

As presented in Table2, 239 cases were received initial treatment, including 64.4% for chemotherapy, two instances for radiotherapy, four for surgery, and 28.5% for combinatory therapy options. Overall, there were 219 patients administered with chemotherapy alone or with rituximab (Table3), 1029 treatment cycles were achieved, and the median cycles for a patient were 5 (range, 1-11). The most common chemotherapy regimen applied in this study was CHOP, accounting for 84.5%, other regimens comprising CVP, BR or oral vp16, and CTX. Due to the heavy financial burden of the family before 2017, when the price decreased, 34.7% of patients were treated without rituximab in this cohort. It was similar between the age under 80 years and over 80 years on the usage of rituximab; however, in the age over 80 years group, dose reduction was occurred in more patients than those aged 70-79 years (45.1% vs. 20.1%, $p < 0.001$).

Survival outcomes

With a median follow-up of 50 months (range, 1 - 102), 101 cases died during the treatment and follow-up; the median PFS and OS were 42.1 months and 96.4 months in total (Figure1). The 2-year PFS and OS

rate of the entire cohort were 53.0% (95% CI: 46.5-59.5) and 65.5% (95% CI: 59.4-71.2) (Figure1). The 5-year PFS and OS were 44.7% (95% CI: 38.0-51.4) and 56.1% (95% CI: 49.4-62.8) (Figure1). Between patients younger and older than 80 years, the 2-y PFS and OS rate were showed no remarked difference (Supplementary figure1), which were 54.5% (95% CI: 47.4-61.6) and 68.0% (95% CI: 61.5-74.5) in the younger group, compared with 45.3% (95% CI: 29.4-61.2) and 52.9% (95% CI: 37.0-68.8) in the older group.

The impact of rituximab on PFS and OS was also evaluated in our study. We found rituximab involved therapy could pronounced improve the OS and PFS for the entire cohort, the 2-y OS rate was 72.9% (95% CI: 65.9-80.1) in the rituximab group and 56.8% (95% CI: 44.5-69.2) in the no-rituximab group, and 5-y OS rate was 63.6% (95% CI: 55.2 - 72.0) vs. 50.1% (37.6-62.6) (Figure2), p 0.008. The 2-y PFS rate was 59.5% (95% CI: 51.7-67.3) in rituximab-containing treatment group and 44.2% (95% CI: 31.9 - 56.5), and 5-y PFS rate was 50.5% (95% CI: 42.1-58.9) vs 40.7% (28.4-53.0) (Figure2), p 0.031. In addition, stratified by age, patients older than 80 could benefit from rituximab both on PFS and OS. In comparison, for younger than 80 years patients, we observed the improvement in PFS and OS from rituximab, but the p values were not significant (Supplementary figure2).

Reduced chemotherapy dose of regimens was frequently delivered in clinical practice for elderly lymphoma patients; in this study, we detected its role on survival outcomes. As shown in Figure3, there was no statistical difference between standard dose and reduced dose groups overall; however, in the younger than 80 years group, reduced dose was associated with remarked shorter OS, the 2-y OS was 74.4% (95% CI: 67.0-81.8) in full dose group in comparison with 67.1% (95% CI: 51.8-82.4) in decreased dose group, p 0.044. Meanwhile, we did not observe the remarked deterioration on PFS or OS in the older than 80 years group with dose reduction (Supplementary figure3).

Additionally, we observed that treatment cycles (chemotherapy $\pm$ rituximab) were associated with survival outcomes. As Figure4 presented, patients treated with six cycles or more obtained a superior OS and PFS than that with less than six cycles, the 2-y PFS were 66.2% vs. 44.5%, p 0.000, and 2-y OS were 77.6% vs. 59.5%, p 0.000. Further subgroup analysis showed that ≥ 6 cycles of R-CHOP/CVP treatment were achieved better PFS and OS than less than six cycles in the cohort, 68.7% and 49.0% for 2-y PFS, p 0.001, 81.0%, and 63.8% for 2-y OS, p 0.000 (Supplementary figure4).

IPI score was frequently applied to predict the prognosis of DLBCL patients. Here, we used IPI score to divide patients into $\text{IPI} \leq 3$ or $\text{IPI} > 3$ groups; as presented in the Figure5, patients with $\text{IPI} \leq 3$ had longer PFS and OS than those with $\text{IPI} > 3$, the 2-y PFS were 58.7% vs. 35.7%, p 0.005; and 2-y OS were 71.5% vs. 47.3%, p 0.001, individually. In younger than 80 years population, the 2-y PFS rate in the group of $\text{IPI} \leq 3$ and of $\text{IPI} > 3$ was 61.2%, 31.8%, p 0.001, the 2-y OS rate in the group of $\text{IPI} \leq 3$ and of $\text{IPI} > 3$ was 74.9%, 44.7%, p 0.000. In ≥ 80 years population, the 2-y PFS rate in group of $\text{IPI} \leq 3$ and of $\text{IPI} > 3$ was 43.6%, 49.0%, p 0.741, the 2-y OS rate in group of $\text{IPI} \leq 3$ and of $\text{IPI} > 3$ was 51.7%, 56.3%, p 0.888 (Supplementary figure5). However, further analysis in patients with the $\text{IPI} = 1, 2, 3, 4, 5$, we only found the

OS difference on the IPI = three vs. IPI = 4 and IPI = 4 vs. IPI = 5 groups (Supplementary figure 6 and supplementary table 1), yet PFS benefit was negative.

In addition, we performed the univariate and multivariate analyses in this study. From the univariate analyses results (Supplementary table 2), ECOG score ≥ 2 (p 0.015), Ann Arbor stage III/IV (p 0.012), IPI score > 3 (p 0.005), treated without rituximab (p 0.002) were associated with poor PFS; while extra nodal involved more than 1 site (p 0.039), ECOG score ≥ 2 (p 0.002), IPI score > 3 (p 0.001) and treated without rituximab (p 0.000) were linked with poor OS. As to the impact of GCB and non-GCB subtype on survival, we found no statistical significance on PFS and OS. In multivariate analyses, Ann Arbor stage III/IV was related to the poor PFS, HR 1.640 (95% CI: 1.031-2.610, p 0.037); dose reduction was associated with the poor OS, HR 1.825 (95% CI: 1.056-3.154, p 0.031), and rituximab usage was related with OS benefit, HR 0.455 (95% CI: 0.264 - 0.785, p 0.005) (Table 4A and 4B).

Toxicity

The data of 187 patients were available to perform safety analysis; the most common adverse effects in this study were hematological toxicities, which accounted for 90.4%, and leukopenia ($<$ lower limit of normal) was the most frequently happened of $\geq$ grade 3 events (Table 5). The severity of treatment-emergent adverse events was similar between groups (Table 6). A higher incidence of fatigue, hypoalbumin were reported in older group, 63.9% vs. 93.1%; 53.8% vs. 89.7%. Whereas thrombocytopenia (any grade) was more common in the younger group, 34.8% vs. 13.8%.

Discussion

To our knowledge, this is the largest series that has analyzed clinical features and survival outcomes in aged ≥ 70 years DLBCL patients in China. The prognosis of this elderly DLBCL population with a 2-y OS rate of 65.5% was better than that reported in China with 42.8%^[12]. Considering two significant reasons that may contribute to the disparity, one was a higher proportion of rituximab usage in our study, 65.3% vs. 53.8%, which significantly impacted the overall survival for this population, including the very elderly DLBCL patients (≥ 80 years). The other was that a larger series of 239 elderly DLBCL patients aged ≥ 70 years in our cohort, whereas 145 cases were included in that study, which may lead to the results bias.

Rituximab could improve the EFS and OS for 60-80 years DLBCL patients^[14, 15]. In this cohort, we found similar results: rituximab increased 2-y OS rate against only CHOP, 72.9% vs. 56.8%, p 0.008; and 2-y PFS 59.5% vs. 44.2%, p 0.031. Further analysis showed this result could continue to be made in the ≥ 80 years subgroup. In the younger than 80 years group, we could see the improvement on the PFS and OS, but the p values were not significant, which may be related to the small sample size. Currently, rituximab is delivered with 375 mg/m² with an interval of every three weeks for 6-8 cycles in the standard regimen; additionally, some studies investigated whether increased dose of rituximab could improve treatment efficacy in elderly patients, showing that 500 mg/m² rituximab enhanced the PFS and OS of elderly male cases compared to the normal dose^[16-18]. Meanwhile, a study from Netherland presented that rituximab

intensification during the first four cycles of R-CHOP14 had no improvement in the complete response rate, 3-y PFS rate, and 3-y OS rate compared with standard R-CHOP14 and increased the toxicities in the patients between ages 66-80 years^[19]. There were no patients administered with this maximum rituximab dose in this study. In clinical practice, it is recommended that eight cycles of R plus six cycles of CHOP21 or six cycles R-miniCHOP in treating elderly DLBCL according to some critical studies results^[15, 20–23]. The median cycles applied with a patient in our cohort were 5, of which 51.5% were administered with less than six cycles of treatment, while 48.5% with six cycles or more. In contrast to usage with ≥ 6 cycles of therapy in our data, patients with less than six cycles had inferior PFS and OS, suggesting the 6 or 8 cycles of treatment is emphasized in clinical practice.

The treatment strategy for elderly DLBCL patients has not been well established. In comparison with R-CHOP14 applied in the 60-80-years old DLBCL patients, R-CHOP21 could attain similar efficacy and decreased frequency and severity of hematological adverse effects and red-blood-cell transfusion, leading the R-CHOP21 as the frequently administered regimen^[21, 24]. In our study, 74.4% of patients were administered with full-dose for those aged 70-79 years and 67.1% for those older than 80 years. R-miniCHOP is recommended in ≥ 80 y cases^[7, 9, 25]. Peyrade F reported that ≥ 80 y European patients treated with R-miniCHOP obtained a 2-y OS rate of 59%, 2-y PFS rate 47%^[9]. From our data, we observed similar results in the Chinese population with a 2-y OS rate of 52.9% and a 2-y PFS rate of 45.3% treated with full dose or reduced dose therapy. Additionally, in our subgroup analysis, we found that reduced chemotherapy dose was not correlated with the 2-y OS rate compared with the standard dose in older than 80 years population, which was comparable to results of some studies ever reported^[9, 25], indicating that reduced chemotherapy dose may balance the efficacy and side effects for this population. However, in patients aged 70-79 years, chemotherapy dose reduction ($\geq 20\%$) could have a worse impact on the OS than those with the full dose, 2-y OS rate 67.1% vs. 74.4%, $p = 0.044$. In line with a previous study result^[26], it reported that 70% of standard dose would affect the OS and EFS in patients aged over 70 years. Taken together, our data suggested that reduced chemotherapy dose exerted survival deterioration for all aged ≥ 70 years patients, except for over 80 years.

DLBCL is divided into GCB, ABC and unclassified subtypes with a gene expressing profile (GEP)^[27]. It also reported that Han's algorithm had prognosis value with the cell of origin (COO) determination^[28]. In our study, we applied the Han's algorithm to divide patients into GCB and non-GCB subtypes. Additionally, Mareschal S et al. reported that ABC subgroup was more common in elderly patients^[29]. In agreement, a similar result was observed in our study with 21.8% of GCB subtype and 61.9% of non-GCB subtype. Lenz reported that GCB subtype has superior PFS and OS rates than ABC subtype with R-CHOP^[30]. Our cohort found that GCB subtype with 2-y PFS rate 63.5% and 2-y OS rate 72.2%, whereas non-GCB subtype with 2-y PFS rate 55.8% and 2-y OS rate 66.5% (data not shown); however, the difference was not significant. Moreover, in the univariate analyses, patients with GCB or non-GCB had similar OS and PFS, associated with the non-GCB dominance in this cohort.

IPI score is a prognostic model widely performed in DLBCL patients. Recently, a study reported that NCCN-IPI had the greatest absolute difference in OS estimates between the highest- and lowest-risk groups and best-discriminated OS compared to the IPI score and the aaIPI for the entire DLBCL cohort^[31]. In our study, NCCN-IPI and aaIPI were not fit for evaluating the prognosis as the included patients were all aged ≥ 70 years. According to the IPI score, there were significant discriminations in PFS and OS between the $IPI \leq 3$ and $IPI > 3$ groups, which remained in the subgroups analysis of younger or older than 80 years patients, suggesting that IPI score could distinguish the prognosis in elderly patients with a high-risk group or not. Moreover, we observed inferior survival outcomes in cases with $IPI=5$ than with $IPI=4$. However, it presented no discriminated PFS and OS in low-risk, low-intermediate, high-intermediate, indicating a prognostic model to evaluate in elderly DLBCL patients is an urgent need. Recently, a study from Italy reported that combined the comprehensive geriatric assessment (CGA) with IPI score could identify three risk groups with the remarked difference in terms of OS^[32, 33]; however, we did not perform this method on our cohort as the CGA lack.

Nonetheless, this study had several limitations. First, our study was retrospective, selection and information bias could not have been avoided. Second, in our research, 34.7% of patients were treated without rituximab, due to the heavy financial burden of the family before 2017, which may exert a deteriorating impact on the whole cohort survival. Third, patients in our study had not done the CGA, which could predict OS and may assist clinicians in determining the treatment with full-dose chemotherapy or not^[34, 35].

Conclusion

This study presented that rituximab improved the PFS and OS for the older than 70 years patients with DLBCL. Additionally, reduced chemotherapy dose had a deteriorated influence on the OS for patients 70-79 years; however, it did not affect the survival outcome of older than 80 years. Furthermore, less than six cycles were related to the inferior OS and PFS. Collectively, rituximab, enough treatment cycles, full chemotherapy dose, and more efficient regimens with lower toxicities should be administered for elderly DLBCL patients under the balance of benefit and risk. To this end, a simplified predictive model to optimize the stratified therapy needs to be explored in the future.

Abbreviations

DLBCL

Diffuse large B-cell lymphoma

PFS

Progression-free survival

OS

Overall survival

EFS

Event-free survival

GCB

Germinal center B-cell

GEP

Gene expressing profile

COO

Cell of origin

CT

Computed tomography scans

PET-CT

Positron emission tomography scans-computed tomography

CGA

Comprehensive geriatric assessment

IPI

International prognostic index

aaIPI

age-adjusted IPI

NCCN-IPI

National Comprehensive Cancer Network prognostic index

Declarations

Ethics approval and consent to participate

The protocol of this retrospective study, involving individuals' clinical data collection, was approved and the need for informed consent was waived by the Ethics Committee of West China Hospital of Sichuan University.

Consent for publication

Not applicable

Availability of data and material (ADM)

All data generated or analyzed during the present study are included in this article. The authors declare that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality. The authors confirmed that all methods were performed in accordance with the relevant guidelines and regulations

Competing interests

The authors declare no competing interests.

Funding

Not applicable.

Authors' contribution

YC and LQ contributed equally to this work. ZL: conception and design. LL, XK, ZY, and HY: administrative support. YC and LQ collected and analyzed data, prepared all the figures and tables. All authors wrote and reviewed the manuscript.

Acknowledgement

The authors thank all those who participated in patient recruitment and helped gather patients' information.

References

1. Al-Hamadani M, Habermann TM, Cerhan JR et al. Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: A longitudinal analysis of the National Cancer Data Base from 1998 to 2011. *Am J Hematol* 2015; 90: 790-795.
2. <https://seer.cancer.gov/statfacts/html/dlbcl.html>.
3. A predictive model for aggressive non-Hodgkin's lymphoma. *The New England journal of medicine* 1993; 329: 987-994.
4. Zhou Z, Sehn LH, Rademaker AW et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood* 2014; 123: 837-842.
5. Choi JH, Kim TM, Kim HJ et al. Multicenter Retrospective Analysis of Clinical Characteristics, Treatment Patterns, and Outcomes in Very Elderly Patients with Diffuse Large B-Cell Lymphoma: The Korean Cancer Study Group LY16-01. *Cancer Res Treat* 2018; 50: 590-598.
6. Tilly H, Gomes da Silva M, Vitolo U et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology* 2015; 26 Suppl 5: v116-v125.
7. <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1480>.
8. Nowakowski GS, Chiappella A, Witzig TE et al. ROBUST: Lenalidomide-R-CHOP versus placebo-R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma. *Future oncology (London, England)* 2016; 12: 1553-1563.
9. Peyrade F, Jardin F, Thieblemont C et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *The Lancet Oncology* 2011; 12: 460-468.
10. Shen Q-D, Zhu H-Y, Wang L et al. Gemcitabine-oxaliplatin plus rituximab (R-GemOx) as first-line treatment in elderly patients with diffuse large B-cell lymphoma: a single-arm, open-label, phase 2

- trial. *The Lancet. Haematology* 2018; 5: e261-e269.
11. Gini G, Tani M, Tucci A et al. Lenalidomide and Rituximab (ReRi) As Front Line Chemo-Free Therapy of Elderly Frail Patients with Diffuse Large B-Cells Lymphoma. a Phase II Study of the Fondazione Italiana Linfomi (FIL). *Blood* 2019; 134 (Supplement_1): 2880. .
 12. Liu P, Han Y, Jiang SY et al. A retrospective analysis of real-world outcomes of elderly Chinese patients with diffuse large B-cell lymphoma. *Chin Med J (Engl)* 2019; 132: 1807-1814.
 13. Swerdlow SH, Campo E, Harris NL et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. International Agency for Research on Cancer (IARC) 69372 Lyon Cedex 08, France 2017.
 14. Bertrand Coiffier, Eric Lepage, Josette Briere et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002; Jan 24;346(4):: 235-242.
 15. Coiffier B, Thieblemont C, Van Den Neste E et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood* 2010; 116: 2040-2045.
 16. He HX, Gao Y, Bai B et al. The beneficial effect of Escalated-R-CHOP-21 for the treatment of diffuse large B-cell lymphoma in elderly male patients: A propensity-matched cohort study. *Cancer Med* 2021.
 17. Pfreundschuh M, Murawski N, Zeynalova S et al. Optimization of rituximab for the treatment of DLBCL: increasing the dose for elderly male patients. *British journal of haematology* 2017; 179: 410-420.
 18. Pfreundschuh M, Poeschel V, Zeynalova S et al. Optimization of rituximab for the treatment of diffuse large B-cell lymphoma (II): extended rituximab exposure time in the SMARTE-R-CHOP-14 trial of the german high-grade non-Hodgkin lymphoma study group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2014; 32: 4127-4133.
 19. Lugtenburg PJ, de Nully Brown P, van der Holt B et al. Rituximab-CHOP With Early Rituximab Intensification for Diffuse Large B-Cell Lymphoma: A Randomized Phase III Trial of the HOVON and the Nordic Lymphoma Group (HOVON-84). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2020; 38: 3377-3387.
 20. Pfreundschuh M, Schubert J, Ziepert M et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *The Lancet. Oncology* 2008; 9: 105-116.
 21. Delarue R, Tilly H, Mounier N et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. *The Lancet Oncology* 2013; 14: 525-533.
 22. Sehn LH, Congiu AG, Culligan DJ et al. No Added Benefit of Eight Versus Six Cycles of CHOP When Combined with Rituximab in Previously Untreated Diffuse Large B-Cell Lymphoma Patients: Results from the International Phase III GOYA Study. *Blood* 2018; 132 (Supplement 1): 783. . 2018.

23. Wüsterlid T, Biccler JL, Brown PN et al. Six cycles of R-CHOP-21 are not inferior to eight cycles for treatment of diffuse large B-cell lymphoma: a Nordic Lymphoma Group Population-based Study. *Annals of oncology : official journal of the European Society for Medical Oncology* 2018; 29: 1882-1883.
24. Cunningham D, Hawkes EA, Jack A et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet (London, England)* 2013; 381: 1817-1826.
25. Eyre TA, Martinez-Calle N, Hildyard C et al. Impact of intended and relative dose intensity of R-CHOP in a large, consecutive cohort of elderly diffuse large B-cell lymphoma patients treated with curative intent: no difference in cumulative incidence of relapse comparing patients by age. *Journal of internal medicine* 2019; 285: 681-692.
26. Meguro A, Ozaki K, Sato K et al. Rituximab plus 70% cyclophosphamide, doxorubicin, vincristine and prednisone for Japanese patients with diffuse large B-cell lymphoma aged 70 years and older. *Leuk Lymphoma* 2012; 53: 43-49.
27. Scott DW, Wright GW, Williams PM et al. Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue. *Blood* 2014; 123: 1214-1217.
28. Hans CP, Weisenburger DD, Greiner TC et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood* 2004; 103: 275-282.
29. Mareschal S, Lanic Hln, Ruminy P et al. The proportion of activated B-cell like subtype among de novo diffuse large B-cell lymphoma increases with age. *Haematologica* 2011; 96: 1888-1890.
30. Lenz G, Wright G, Dave SS et al. Stromal gene signatures in large-B-cell lymphomas. *The New England journal of medicine* 2008; 359: 2313-2323.
31. Ruppert AS, Dixon JG, Salles G et al. International prognostic indices in diffuse large B-cell lymphoma: a comparison of IPI, R-IPI, and NCCN-IPI. *Blood* 2020; 135 (23): 2041–2048. .
32. Spina M, Merli F, Puccini B et al. Definition and Validation of the New Elderly Prognostic Index (EPI) for Elderly Patients with Diffuse Large B-Cell Lymphoma Integrating Geriatric and Clinical Assessment: Results of the Prospective "Elderly Project" on 1353 Patients By the Fondazione Italiana Linfomi. *Blood* 2019; 134 (Supplement_1): 398. .
33. Merli F, Luminari S, Tucci A et al. Simplified Geriatric Assessment in Older Patients With Diffuse Large B-Cell Lymphoma: The Prospective Elderly Project of the Fondazione Italiana Linfomi. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2021; 39: 1214-1222.
34. Hamaker ME, Prins MC, Stauder R. The relevance of a geriatric assessment for elderly patients with a haematological malignancy—a systematic review. *Leukemia research* 2014; 38: 275-283.

35. Lin RJ, Behera M, Diefenbach CS, Flowers CR. Role of anthracycline and comprehensive geriatric assessment for elderly patients with diffuse large B-cell lymphoma. Blood 2017; 130: 2180-2185.

Tables

Table1. Clinical characteristics of 239 Chinese elderly patients (age≥70 years) with DLBCL at diagnosis.

Parameters	All patients n=239	70-79 years n=200	≥80 years n=39	<i>p</i> value
Median age	75.4 (70-91)	74.0 (70-79)	82.6 (80-91)	
Sex				0.341
Male	143 (59.8%)	117 (58.5%)	26 (66.7%)	
Female	96 (40.2%)	83 (41.5%)	13 (33.3%)	
ECOG score				0.507
0-1	193 (80.8%)	163 (81.5%)	30 (76.9%)	
≥2	46 (19.2%)	37 (18.5%)	9 (23.1%)	
B symptoms				0.527
Yes	174 (72.8%)	144 (72.0%)	30 (76.9%)	
No	65 (27.2%)	56 (28.0%)	9 (23.1%)	
Subtype				0.759
GCB	52 (21.8%)	44 (22.0%)	8 (20.5%)	
non-GCB	148 (61.9%)	122 (61.0%)	26 (66.7%)	
Unknown	39 (16.3%)	34 (17.0%)	5 (12.8%)	
Ki-67 index				0.784
>90%	7 (2.9%)	6 (3.0%)	1 (2.6%)	
≤90%	192 (80.3%)	162 (81.0%)	30 (76.9%)	
Unknown	40 (16.7%)	32 (16.0%)	8 (20.5%)	
Number of extra-nodal involvement				0.084
0 or 1	174 (74.5%)	150 (75.0%)	24 (61.5%)	
≥2	65 (27.2%)	50 (25.0%)	15 (38.5%)	
Bone marrow involvement				0.442
Yes	12 (5.0%)	11 (5.5%)	1 (2.6%)	
No	227 (95%)	189 (94.5%)	38 (97.4%)	
Ann Arbor stage				0.191
I-II	96 (40.2%)	84 (42.0%)	12 (30.8%)	
III-IV	143 (59.8%)	116 (58.0%)	27 (69.2%)	

Bulky disease				0.565
Yes	38 (15.9)	33 (16.5%)	5 (12.8%)	
No	201 (84.1%)	167 (83.5%)	34 (87.2%)	
Serum LDH				0.900
Normal	102 (42.7%)	85 (42.5%)	17 (43.6%)	
Elevated	137 (57.3%)	115 (57.5%)	22 (56.4%)	
IPI score				0.299
1	52 (21.8%)	44 (22.0%)	8 (20.5%)	
2	61 (25.5%)	55 (27.5%)	6 (15.4%)	
3	65 (27.2%)	54 (27.0%)	11 (28.2%)	
4-5	61 (25.5%)	47 (23.5%)	14 (35.9%)	
Comorbidities				0.784
Yes	205 (85.8%)	171 (85.5%)	34 (87.2%)	
No	34 (14.2%)	29 (14.5%)	5 (12.8%)	

ECOG: eastern cooperative oncology group. GCB: germinal center B-cell like. LDH: lactate dehydrogenase. IPI: international prognostic index.

Table2. Initial treatment regimens of Chinese elderly patients with DLBCL (n=239).

Parameters	All patients n=239	70-79 years n=200	≥80 years n=39	<i>p</i> value
Therapy options				0.794
Chemotherapy	154 (64.4%)	128 (64.0%)	26 (66.7%)	
Radiotherapy	2 (0.8%)	1 (0.5%)	1 (2.6%)	
Surgery	4 (1.7%)	3 (1.5%)	1 (2.6%)	
Chemotherapy +Radiotherapy	27 (11.3%)	24 (12.0%)	3 (7.7%)	
Surgery +Chemotherapy	29 (12.1%)	25 (12.5%)	4 (10.3%)	
Surgery +Radiotherapy	3 (1.3%)	2 (1.0%)	1 (2.6%)	
Surgery +Chemotherapy +Radiotherapy	9 (3.8%)	7 (3.5%)	2 (5.1%)	
Untreated	11 (4.6%)	10 (5.0%)	1 (2.6%)	
Rituximab				0.350
Yes	156 (65.3%)	128 (64.0%)	28 (71.8%)	
No	83 (34.7%)	72 (36.0%)	11 (28.2%)	
Dose reduction of chemotherapy				<0.001
Yes	53 (22.2%)	37 (18.5%)	16 (41.0%)	
No	147 (61.5%)	135 (67.5%)	12 (30.8%)	
Unknown	39 (16.3%)	28 (14.0%)	11 (28.2%)	

Table3. Chemotherapy of Chinese elderly patients with DLBCL (n=219).

Parameters	All patients n=219	70-79 years n=184	≥80 years n=35	<i>p</i> value
Rituximab				0.211
Yes	156 (71.2%)	128 (69.6%)	28 (80.0%)	
No	63 (28.8%)	56 (30.4%)	7 (20.0%)	
Regimens				0.004
CHOP	185 (84.5%)	162 (88.0%)	23 (65.7%)	
CVP	15 (6.8%)	10 (5.4%)	5 (14.3%)	
Others	19 (8.7%)	12 (6.5%)	7 (20.0%)	
Chemotherapy dose reduction				<0.001
Yes	53 (24.2%)	37 (20.1%)	16 (45.7%)	
No	147 (67.1%)	135 (73.4%)	12 (34.3%)	
Unknown	19 (8.7%)	12 (6.5%)	7 (20.0%)	
Therapy cycles				0.740
<6	112 (51.1%)	95 (51.6%)	17 (48.6%)	
≥6	107 (48.9%)	89 (48.4%)	18 (51.4%)	
Prophylaxis with G-CSF				0.060
Yes	44 (20.1%)	32 (17.4%)	22 (62.9%)	
No	161 (73.5%)	139 (75.5%)	12 (34.2%)	
Unknown	14 (6.4%)	13 (7.1%)	1 (2.9%)	

G-CSF: granulocyte colony-stimulating factor.

Table 4A. Multivariate analysis of PFS in 239 Chinese elderly patients with DLBCL.

Parameters	β	SE	Wald	HR	95% CI	<i>p</i> value
Stage III/IV	0.495	0.237	4.358	1.640	1.031-2.610	0.037
ECOG score ≥ 2	0.232	0.258	0.807	1.261	0.760-2.092	0.369
Serum LDH >normal	0.073	0.213	0.117	1.076	0.708-1.634	0.733
Extranodal involvement > 1 site	-0.020	0.236	0.008	0.980	0.616-1.557	0.931
B symptoms	0.144	0.218	0.440	1.155	0.754-1.770	0.507
Bone marrow involvement	0.129	0.455	0.080	1.137	0.466-2.774	0.777
Rituximab	-0.475	0.213	4.984	0.622	0.410-0.944	0.026

Table4B. Multivariate analysis of OS in 239 Chinese elderly patients with DLBCL.

Parameters	β	SE	Wald	HR	95% CI	<i>p</i> value
Stage III/IV	0.137	0.294	0.215	1.146	0.644-2.041	0.643
ECOG score ≥ 2	0.121	0.337	0.129	1.129	0.583-2.188	0.719
Serum LDH >normal	-0.063	0.267	0.056	0.939	0.556-1.585	0.813
Extranodal involvement > 1 site	0.236	0.291	0.656	1.266	0.716-2.237	0.418
B symptoms	0.364	0.274	1.771	1.440	0.842-2.463	0.183
Bone marrow involvement	0.243	0.640	0.144	1.275	0.363-4.473	0.704
Dose reduction	0.602	0.279	4.650	1.825	1.056-3.154	0.031
Rituximab	-0.787	0.278	8.016	0.455	0.264-0.785	0.005

Table5. Summary of adverse events (n=187).

Parameters	All patients n=187	70-79 years n=158	≥80 years n=29
Anemia	146 (78.1%)	126 (79.7%)	20 (69.0%)
Leukopenia	149 (79.7%)	127 (80.4%)	22(75.9%)
Neutropenia	128 (68.4%)	109 (69.0%)	19 (65.5%)
Febrile neutropenia	26 (13.9%)	20 (12.7%)	6 (20.7%)
Thrombocytopenia	59 (31.6%)	55 (34.8%)	4 (13.8%)
Thrombus	9 (4.8%)	8 (5.1%)	1 (3.4%)
Fatigue	111 (59.4%)	85 (53.8%)	26 (89.7%)
Nausea/vomiting	148 (79.1%)	122 (77.2%)	26 (89.7%)
Hypo-albumin	128 (68.4%)	101 (63.9%)	27 (93.1%)
Aspartate aminotransferase increased	59 (31.0%)	51 (32.3%)	8 (27.7%)
Elevated creatinine	13 (5.9%)	10 (6.3%)	1 (3.4%)
Neuro-toxicities	6 (3.2%)	6 (3.8%)	0
Cardio-toxicities	11 (5.9%)	10 (6.3%)	1 (3.4%)
Death during treatment	28 (15.0%)	20 (12.7%)	8 (27.6%)

Table6. Summary of ≥ grade 3 hematological adverse events (n=187).

Parameters	All patients n=187	70-79 years n=158	≥80 years n=29
Anemia	23 (12.3%)	22 (13.9%)	1 (3.4%)
Leukopenia	76 (40.6%)	62 (39.2%)	14 (48.3%)
Neutropenia	71 (38.0%)	57 (36.1%)	14 (48.3%)
Febrile neutropenia	26 (13.9%)	20 (12.7%)	6 (20.7%)
Thrombocytopenia	15 (8.0%)	14 (8.9%)	1 (3.4%)
Total	94 (50.3%)	78 (49.4%)	16 (55.2%)

Figures

Figure 1
(n=239). Kaplan-Meier survival curve of progression-free survival and overall survival of 239 DLBCL patients. The 2-y PFS and 2-y OS were 53.0% (95% CI: 46.5-59.5) and 65.5% (95% CI: 59.4-71.2), the 5-

year PFS and OS were 44.7% (95% CI: 38.0-51.4), 56.1% (95% CI: 49.4-62.8), and the median PFS and media OS were 42.1 months and 96.4 months.

Figure 2
(n=219). Kaplan-Meier survival curve of PFS and OS for elderly patients with DLBCL stratified by rituximab usage. The 2-y PFS rate in rituximab-containing treatment group and without rituximab group

was 59.5%, 44.2%, p 0.031; the 2-y OS rate in rituximab-containing treatment group and without rituximab group was 72.9%, 56.8%, p 0.008.

Figure 3

(n=200). Kaplan-Meier survival curve of PFS and OS for elderly patients with DLBCL stratified by reduced chemotherapy dose. The 2-y PFS rate in group of reduced chemotherapy dose and in group of standard dose was 56.0%, 60.1%, p 0.384, the 2-y OS rate in group of reduced chemotherapy dose and in group of standard dose was 67.3%, 73.7%, p 0.139.

Figure 4

(n=219). Kaplan-Meier survival curve of PFS and OS for elderly patients with DLBCL stratified by chemotherapy cycles. The 2-y PFS rate in group of < 6 chemotherapy cycles and in group of ≥ 6 cycles was 44.5%, 66.2%, p 0.000, the 2-y OS rate in group of in group of < 6 chemotherapy cycles and in group of ≥ 6 cycles was 59.5%, 77.6%, p 0.000.

Figure 5

(n=239). Kaplan-Meier survival curve of PFS and OS for elderly patients with DLBCL stratified by IPI score. The 2-y PFS rate in group of $IPI \leq 3$ and of $IPI > 3$ was 58.7%, 35.7%, p 0.005, the 2-y OS rate in group of $IPI \leq 3$ and of $IPI > 3$ was 71.5%, 47.3%, p 0.001.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplementaryfigures.docx](#)
- [supplementarytables.docx](#)