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ORIGINAL ARTICLE

Clinical characteristics, treatment patterns and outcomes of patients older than 80 years diagnosed with DLBCL in China over a 10-year period

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Abstract

Purpose The treatment strategy for elderly patients older than 80 years with DLBCL has not been defined yet because of poor treatment tolerability and lack of data. The aim of this trial was to retrospectively investigate clinical characteristics, treatment patterns and outcomes of patients older than 80 years diagnosed with DLBCL in China over a 10-year period.

Methods This trial comprised 57 patients, aged ≥ 80 years, who were initial diagnosed as diffuse large B-cell lymphoma from 2007 to 2017. They received at least four cycles of reduced-dose R-CHOP21 (Rituximab 375 mg/m^2 day 0, Cyclophosphamide 400 mg/m^2 day1, Epirubicin 35 mg/m^2 day 1, Vincristine 1 mg day 1, and Prednisone 50 mg/m^2 days 1–5). An observational population-based, cohort study was performed.

Results The median age was 82.5 years (range 80–90 years) and the overall response rate was 73.7%. With a median 36.4-month follow-up, 2-year overall survival (OS) and 2-year progression-free survival were 74.3% and 70.9%, respectively. Using rigorous multivariate analysis, we concluded that NCCN-IPI ≥ 5 was the only predictive poor prognostic factor.

Conclusions High response rate was concluded on very elderly DLBCL patients (≥ 80 years old) with reduced-dose R-CHOP. However, the very elderly patients with NCCN-IPI score ≥ 5 would lead to poor outcome.

Keywords Diffuse large B-cell lymphoma · Very elderly · Aged · R-CHOP

Introduction

China, as well as other developing countries, is facing dramatic demographic changes, with a continuously increasing proportion of elderly patients in the society due to a combination of lower birth rate and continuously rising life expectancy. The threshold age of 80 years has been defined as the cut-off value for very elderly patients considering the fact that individuals younger than 80 years are usually recognized to have good tolerance and efficacy. Currently, population-based studies have reported that DLBCL (Diffuse Large B-cell Lymphoma) is the most common subtype of NHL (Non-Hodgkin's Lymphoma), with a rising incidence of 112 per 100,000 in those of 80–84 years old [1]. These expected continuously increasing numbers in the very elderly DLBCL warrant a determination of current decision-making patterns and a greater demand for the most effective management strategies in this population.

Hitherto, a major subset of DLBCL patients was proved to be cured by the standard immune-chemotherapy with R-CHOP21 [2]. Nevertheless, the outcome of ≥ 80 very elderly patients with lymphoma is worse because of the difficulties encountered during treatment and the difficulties related to the higher prevalence of comorbidities, decreased physiological reserve, diminished functional capacity, cognitive impairment, and altered drug metabolism. However, very elderly patients with DLBCL are seldom enrolled in most large randomized clinical trials because ethically or technically unfeasible, and to date evidence-based treatment algorithms and recommendations for very elderly patients with lymphoma are still missing.

To our knowledge, cohort study from a population-based registry, with emphasis on the treatment patterns and

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survival in the very elderly, has not been conducted yet in China. Our study sought to analyze presentation, survival patterns and evaluate the feasibility of using the reduced-dose R-CHOP (RD R-CHOP) in a population-based cohort to identify the optimal regimen for treating very elderly DLBCL patients in China.

Materials and methods

Patients selection and data collection

The trial was a prospective, non-interventional, single institution, cohort study. This study was approved by the institutional review board at Hua'Dong Hospital of Shanghai, China. Informed consents were obtained from all individual participants included in the study.

The inclusion criteria of the study were (a) patients equal to or over 80 years of age who had been diagnosed with de novo DLBCL according to the WHO classification [3] between July 2007 and December 2017; (b) patients who had received at least four cycles of R-CHOP; and (c) patients with a history of other malignant diseases, recurrent DLBCL, primary central nervous system lymphoma, primary cutaneous DLBCL or Richter's DLBCL, and hepatitis B virus(HBV) copy number exceeded 10^5 were excluded. DLBCL was pathologically diagnosed made on the lymph nodal biopsy. All histological diagnoses were reviewed by a panel of three experienced pathologists.

Clinical features and treatment records of patients were electronically collected and retrospectively analyzed from the medical data center of Hua'Dong Hospital. All patients were included in the analysis of survival outcomes and feasibility also. Follow-up was completed until 31 Oct 2018. Patient-specific data collection procedures included age; sex; presence of comorbidities; B symptoms, lactate dehydrogenase (LDH); Eastern Cooperative Oncology Group performance status (ECOG- PS); number of extra-nodal sites; site of extra-nodal disease; staging system (carried out according to the Ann Arbor system); cell-of-origin (COO); complete blood count; serum albumin concentration; bone marrow(BM) biopsy; electrocardiogram(ECG); echocardiography (ECHO with evaluation of left ventricular ejection fraction, LVEF); chest, abdomen, pelvis and neck computed tomography (CT); magnetic resonance imaging(MRI) or 18F-2-deoxy-2-Xuoro-D-glucosepositron emission tomography (18 FDG-PET), etc. Serology screening should be carried out for hepatitis B and hepatitis C serology. Bulky disease was defined by the presence of a nodal mass larger than 7.5 cm. Hypoalbuminemia was defined as < 35 g/L [4]. The cut-off value for anemia was been fixed at 12 g/dL. The renal insufficiency had been defined as a serum creatinine level upper than 133 umol/L (1.5 mg/dL).

The main use of the IPI (International Prognostic Index) score has been in the context of clinical trials, allowing risk-stratification of patients and facilitating comparison of results across trials [5], but it does not stratify the very elderly (≥ 80 years) group. The new National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI), with age of ≥ 75 years and higher LDH (> triple) considered as the most important prognostic factors [6, 7], is more suitable for the prognosis analysis of lymphoma in the elderly over 80 years old [8, 9].

Additionally, B-cell IHC markers or immune-histochemical characteristics (e.g., germinal center B-cell type or not) were mandatory by including CD20, CD22, CD79a and CD10. Cell-of-orgin was classified by the immunohistochemistry (IHC)-based Hans algorithm which, according to gene-expression profiling, separates the better prognostic germinal center B-cell (GCB) subtypes and the poorer prognostic activated B-cell (ABC) subtypes. The concurrent IHC expression of both MyC and Bcl-2 or Bcl-6 collected before treatment was proved to be associated with a poor prognosis [10].

Currently, it is crucial that regimen decision-making for elderly patients with lymphoma depends on aspects of the aging process including judgement of comorbidities, malnutrition and impairments in functional capacities. Geriatric assessment was also able to predict severe treatment-related toxicity and overall survival (OS) in a variety of tumors and treatment settings, and could help to tailor the treatment choice and intensity in each individual. To quantify comorbidity, the Modified-Cumulative Illness Rating Scale (M-CIRS) score is one of the most widely available scores for measuring the complication diseases, including fourteen systems. The severity of each system disease is equally divided into 5 levels, scored 0–4 from low to high severity level [11].

The immuno-chemotherapy regimen and dose adjustments

Emerging data suggest that full-dose intensity R-CHOP21 may be detrimental for the very elderly (> 80 years) DLBCL patients with no existing comorbidities [12, 13]. In the search for optimal therapy of very elderly or frail DLBCL patients, it has been reported that very elderly patients need predominantly to reduce the dose [14–18]. Among these, R-mini CHOP regimen showed good results of both efficacy and safety, which are supported by the encouraging results of GELA LNH03-7B [19]. In this GELA LNH03-7B multicenter, single-arm trial, the 149 elderly patients > 80-years-old were treated with the low-dose R-CHOP21 (R-mini-CHOP) regimen. The median overall survival was 29 months with a 62% complete remission and unconfirmed complete remission rate and only 12 treatmentrelated deaths, which

demonstrated that the R-mini-CHOP21(Rituximab 375 mg/m^2 on Day 0, Cyclophosphamide 400 mg/m^2/div on Day 1, Doxorubicin 25mg/m^2/div on Day 1, Vincristine 1mg/div on Day 1, and Prednisone 40 mg/m^2/d infusion on Days 1–5) had significantly improved the outcome of > 80-year-old patients with the controllable treatment-related toxicity [19, 20]. Moreover, the age setting and the regimen dose of current cohort were consistent with those of GELA LNH03-7B study. In our trial, all patients were planned to receive the front-line RD-RCHOP21 regimen ± radiotherapy which consisted of full dose of Rituximab (375 mg/m^2) on day 0, followed immediately by starting dose level consisting of Cyclophosphamide (CTX) 400 mg/m^2/days iv on day 1, Epirubicin 35 mg/m^2/days iv on day 1, Vincristine(VCR) 1 mg/days iv on day 1, and Methylprednisolone 50 mg/m^2/days infusion on days 1–5. The combination therapy was administered at 3-week intervals, and each received a minimum of four cycles. Regarding the cohort of vulnerable very elderly patients with comorbidities and organ dysfunction like cardiovascular disease, with the LVEF of 68% patients of the cohort lower than 65%, Epirubicin was chosen in this trial, the same isomer of Doxorubicin, but cardiac toxicity is less. Meanwhile, the dosage of Epirubicin was slightly reduced because of the physiological difference between eastern and western. The dose of VCR was the same as that of LNH03-7B trial which serves as key component of R-CHOP. Although the methylprednisolone might increase susceptibility to infections and other adverse reactions, it also played an important role in the therapy of malignant lymphoma. Therefore, we slightly reduced the dosage of methylprednisolone to achieve the purpose of maximizing the efficacy and tolerability. The indication for consolidation involved-field radiotherapy was initial Bulky or extra-nodal disease, since it improved outcomes for elderly patients in this setting. If the testis or breast involved, Methotrexate (MTX) prophylaxis was intended to prevent Central Nervous System (CNS) relapse according to the ESMO and NCCN guidelines.

The multi-agent chemotherapy was administered if neutrophil counts were $\geq 1.5 \times 10^9$/L, platelet counts were $\geq 75 \times 10^9$/L, and all non-hematologic toxicities except nausea and alopecia were alleviated to grade 0 or 1 between cycles. If these results were not achieved, the therapy was postponed for up to 2 weeks until the patients recovered from these toxicities. The dosages of cytotoxic drugs (Cyclophosphamide and Epirubicin) were reduced by 25% in the next cycle if grade 4 neutropenia or thrombocytopenia was developed. The development of grade 2 motor or sensory toxicity required a 25% reduction of the original dose of Vincristine and 50% for grade 3 neurotoxicity. Patients received G-CSF (granulocyte colony-stimulating factors) if they experienced either grade 4 or febrile neutropenia during treatment to minimize myelosuppression and subsequent infectious complications, not only to reduce morbidity and mortality but also to allow complete delivery of the therapy.

Patients with chronic hepatitis or HBV surface antigen (HBsAg) positive were treated by oral Lamivudine or Entecavir for prevention and monitored for HBV-DNA copy number during the trial. When HBV-DNA copy number exceeded 10^5, the use of Rituximab was terminated.

Measurement of ADI and RDI

The Actual Dose Intensity (ADI) and relative dose intensity (RDI) of the average of each drug were calculated at each cycle of RD R-CHOP21. ADI (mg/m^2.week) was calculated by dividing the total received dose of the agent by the number of weeks of treatment [21]. RDI was defined as the ratio of received dose intensity (mg/m^2/week) related to theoretical dose intensity (according to standard 3-week interval) × 100% [22, 23].

Evaluation of response

Tumor responses were assessed after 4 cycles of immune-chemotherapy and at the end of treatment. CT scans or 18FDG-PET was performed to confirm the response. Bone marrow biopsy was repeated at the end of treatment for those patients with bone marrow involvement on entry into the trial. Tumor responses were classified according to the Resist 1.1 [3]. Response assessment in terms of complete remission (CR), unconfirmed complete remission (CRu), partial remission (PR), stable disease (SD) and progressive disease (PD) was performed according to the International Workshop Criteria [3]. The primary endpoint was overall response rate (ORR), and the secondary endpoint was OS, PFS (Progression-free survival). ORR = CR + CRu + PR. OS was measured from the start of diagnosis of DLBCL to the date of death from any cause or the last follow-up at which the patient was known to be alive [24]. PFS was the time that passes from the first day of diagnosis and the date on which disease progresses or the date on which the patient dies, from any cause.

Statistical analysis

All statistical analyses were performed using SPSS software (version 11.0). Survival curves were calculated using the Kaplan–Meier method. Univariate analysis with the log-rank test was used to evaluate prognostic variables for OS. Multivariate analysis was performed using the Cox proportional hazard regression model. All reported p values are 2-sided; p value of 0.05 or less was considered as statistically significant.

Results

Clinical characteristics

Clinical features and treatment records of 67 patients ≥ 80 years who were diagnosed with de novo DLBCL were collected from our institution since 2007–2017. Among these 67 patients, five patients were not included in this observation for receiving less than four cycles of chemo, three patients were not included for a history of other malignant diseases, one primary central nervous system lymphoma patient and one patient refused to the further treatment who did not have sufficient clinical data to calculate the clinical parameters were excluded from analysis.

Consequently, a total of 57 patients (≥ 80 years) were enrolled in this trial from July 2007 to Dec 2017 and no one was lost. These 57 patients, with a median age of 82.5 years (range 80–90 years) who had been diagnosed with de novo DLBCL, were assessable with slightly more female patients (52.7%). The baseline characteristics and pretreatment details of patients are summarized in Table 1. The tumor burden of this cohort was relatively high. Among these, advanced disease (Ann Arbor stage III–IV) was seen in 43 (75.5%) of the cases and high-risk group (NCCN-IPI ≥ 4) was in 51 (89.5%) of the patients.

In this cohort, 96.5% cases had at least one comorbidity. The average M-CIRS score was 6.81(range 2–16) and 33 (57.9%) cases had a score 6 or more M-CIRS in this trial. The most common comorbidities were cardiopathy (73%) (including arrhythmia, valvulopathy cardiac failure, pacemaker), followed by angiopathy (67%) (hypertension), chronic pulmonary disease (42%) (obstructive chronic bronchitis, asthma, pulmonary hypertension), type II diabetes mellitus (37%), chronic liver disease (19%), and cerebrovascular disease (9%). A previous history of renal disease was reported in six cases (10.5%), of whom four did not receive any treatment or received corticosteroids only.

Treatment: delivered cycles and dose intensity of the first-line treatment

Elderly patients often present with alterations of pharmacokinetics of drugs modifying the pharmacodynamics of molecules with change of lean body mass, hepatic and renal function [25]. Thereby, the dosage of cytotoxic drugs should be tailored to creatinine clearance, liver function, and hematopoietic reserve. A decrease in chemotherapy drug, however, has been found to be associated with a lower treatment efficacy [26]; whereas, too aggressive

Table 1 Clinical characteristics of 57 patients

Characteristics	No. of patients	%
Gender		
Male	27	47.3
Female	30	52.7
Age, average(range)	82.5 (80–90)	
80–84	48	84.2
85–89	8	14.0
≥ 90	1	1.8
Cell-of-origin		
GCB subtypes	32	56.1
ABC subtypes	25	43.9
MyC+	11	19.3
Bcl-2+	21	36.8
Bcl-6+	7	12.3
ECOG-PS		
0–1	48	84.2
2	9	15.8
Ann Arbor stage		
I–II	14	25.5
III	12	21.1
IV	31	54.4
B symptom presence	18	31.6
LDH elevated	20	35.1
Hypoalbuminemia	32	56.1
Bone marrow involvement	1	1.8
Anemia	18	31.6
Renal failure	21	36.8
LVEF ≤ 65%	39	68.4
No. of extra-nodal sites		
0	21	36.8
1	31	54.4
≥ 2	5	8.8
Extra-nodal sites	45	
Nasopharyngeal	5	8.8
Oropharynx	7	12.3
Intracranial	1	1.7
Breast	2	3.5
Subcutaneous	5	8.8
Lung	1	1.7
Gastric	2	3.5
Liver	1	1.7
Kidney	1	1.7
Colon	1	1.7
Small intestine	1	1.7
Testis	6	10.5
Bone	6	10.5
Pelvic cavity	6	2.5
Bulky disease	2	3.5
NCCN-IPI risk group		
Low-Intermediate: 2–3	6	10.5
High-intermediate: 4–5	46	80.7

Table 1 (continued)

Characteristics	No. of patients	%
High ≥ 6	5	8.8
M-CIRS median (range)	6 (2–16)	
0–5	25	43.9
≥ 6	33	57.9

Table 2 Relative dose intensity and actual dose intensity

Agent	Relative dose intensity %		Actual dose intensity mg/(m^2 week)	
	Range	Average	Median	Average
Cyclophosphamide	67.4–100.0	91.9	94.0	126.4
Epirubicin	60.7–100.0	81.9	82.2	9.1
Vincristine	83.7–100.0	96.4	91.3	0.3
Prednisone	80–100	90.4	90	86.8

treatments may result in treatment-related morbidity and mortality, and compromise quality of life.

Our observed percentages of adaptations of treatment from the real world were higher than those reported in trials and retrospective studies [16]. Dose adaptation was performed by the discretion and clinical view of the treating physician. Overall, the doses of chemotherapy were reduced for 49 (86.0%) patients in 277 of all 323 first-line therapy cycles. Table 2 shows the average ADI and RDI for five drugs of the RD-RCHOP regimen in all the cohort patients. The planned dose of Rituximab was delivered in 100% of cycles. The average RDI was 81.9% for Epirubicin, 91.9% for Cyclophosphamide, and 96.4% for Vincristine. However, the RDIs of prednisone were about 90% because of poor glucose control which was reduced to 60 mg/day days 1–2 (Table 2). For about a quarter of 67 patients in the cohort, the dosage of Epirubicin was reduced by more than 10%; while for only seven people, the CTX and VCR dosage was reduced by more than 10%. We compared the ORR and survival according to RDI for RD R-CHOP (80% vs < 80% of all drugs). The ORR was significantly lower for high RDI group (42.5%, $n=37$) than for low RDI group (76.6%, $n=20$). The median survival was also significantly shorter for high RDI group than for low RDI group (16.4 months vs 27.4 months). The reasons of these findings may be explained that high RDI group presented higher treatment interruption rate and inadequate treatment cycles which were unfavorable for survival. Among the 57 patients, 26(45.6%) cases finished the 4–5 cycles of the treatment regimen, while 31 (54.4%) cases finished the 6–8 cycles. The median number of cycles administered per patient was 5.7 (range, 4–11). Of the total 323 cycles, 207(64.1%) were delivered on time, at the planned dosage. Among these patients, the RD R-CHOP treatment was unexpectedly discontinued in 7 patients (12.3%) owing to toxicities ($n=3$), disease progression ($n=2$), death ($n=1$), patient's request ($n=1$). Furthermore, consolidation radiotherapy was at the discretion of the physician and performed in 15 patients (26.3%), with one Bulky. The radiotherapy dosage was about 36–40 Gray (Gy) and 2 Gy/f. Five cases were received MTX prophylaxis which intended to prevent CNS relapse when the testis or breast involved.

Toxicities of the first-line treatment and treatment-related mortality

Thus, the therapeutic goal in treating very elderly DLBCL patients is to balance between efficacy and toxicity of treatment. Very elderly patients remain vulnerable to the toxicities of therapies, since they frequently have comorbidities including diminished cardiac and renal function, as well as alterations in drugs absorption, distribution, detoxification, metabolism, and clearance, which modify the pharmacodynamics of the therapeutics. Because of decreased liver function and hematopoietic reserve capacity, the metabolism of cytotoxic drugs such as cyclophosphamide or anthracyclines may be altered [27]. All treatment-related toxicity was retrieved from the hospital files and classified according to common toxicity criteria (CTCAE) [28]. Prophylactic antibiotics were not routinely used.

About two-thirds of this cohort experienced at least one toxicity. The most treatment-related toxicity was notably hematologic toxicity, in which is most of neutropenia, reported in 21(36.8%) cases, 16 (28.1%) of whom experienced grade ≥ 3 toxicity. The median duration of grade 4 neutropenia was 3.6 days (range, 2–6 days). We also found that ≥ 80-year-old patients were less likely to develop febrile neutropenia but more likely to be hospitalized post-treatment. Neutropenic fever was reported in 10 cases (17.5%), while G-CSF was offered in 16 patients (28.1%). Proven infection was documented in 27 cases (47.3%), mainly of bacterial origin. Pneumonia was the most common infectious complication. The incidence of grade ≥ 3 toxicity of anemia and thrombocytopenia was relatively lower than that of neutropenia (14.0% and 22.8%, respectively). In total, 8 (14.0%) patients required blood product support during treatment. Severe non-hematologic toxicities were not as frequent as the hematologic toxicity. Grade ≥ 3 toxicities consisted of sensory neuropathy in 5 (8.8%) cases, liver dysfunction in 4 (7.0%) cases, and renal dysfunction in 3 (5.3%). No Grade ≥ 4 severe cardiotoxicities, or gastro-intestinal toxicities were observed.

Above all, 2(3.5%) cases of treatment-related first-line treatment mortalities occurred, in which one was neutropenic fever following septicemia and one was tumor lysis syndrome; both occurred during the first cycle of therapy.

Treatment outcome with the first-line treatment and salvage treatment

This study demonstrates that the ORR of this cohort was 73.7% (CR, 15; PR, 27; SD, 10; PD, 5). Among the 5 PD cases and 15 relapsed cases after first-line therapy, 16 patients received salvage second-line therapy including dose attenuation of rituximab with gemcitabine, dexamethasone and cisplatin (R-GDP) or rituximab with ifosfamide, carboplatin and etoposide (R-ICE) with ten patients treated with various salvage chemotherapies only, and six patients treated with chemotherapy combined with radiotherapy. The other three patients took Chinese tradition medicine and the one palliative best supportive treatment(BST). Then, seven patients received third-line treatment such as rituximab with gemcitabine and oxaliplatin (R-GemOx) or lenalidomide (Diagram of treatment and response of 57 patients in Fig. 1). The ORR for the salvage therapy was 28.6%. The decision to forgo treatment was based on the poor performance or treatment refusal. The ORR was 22/31(71.0%) for cases who completed 6 cycles, 20/26(76.9%) for those treated with under six-cycle immune-chemotherapy. Therefore this study demonstrated that ORR might not obviously related to the six cycles of treatment or not.

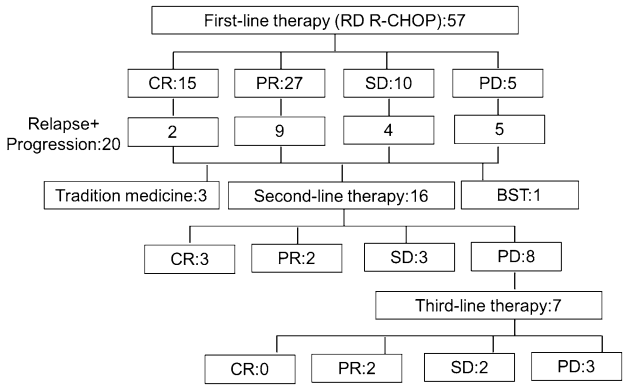

Fig. 1 Diagram of treatment and response of 57 patients in this cohort. *RD* reduced dose, *CR* complete response, *PR* response, *SD* stable disease, *PD* progressive disease. *BST* best supportive treatment

Till the last follow-up in Oct 2018, there were 39 (68.4%) patients still known to be alive, of whom 35 (61.4%) were still alive without progression. In the death of 18 patients, the most causes of death were septic shock ($n=12$), followed by pneumonia ($n=3$), fatal cardiac failure ($n=2$) and tumor lysis syndrome($n=1$).

At the time of this analysis, the median follow-up duration was 36.4 months (range 1.9–117^{+}months). Of 57 patients treated with RD-RCHOP, the favorable median OS was 28.4 months. 2-year PFS rate was 70.9% ± 6.6% and the 2-year OS rate was 74.3% ± 6.2%. The 3-year PFS rate was 68.2% ± 6.9% and the 3-year OS rate was 69.5% ± 6.7% (OS and PFS for this cohort in Fig. 2). The median of 2-year OS was 36.5% for cases who completed six cycles, while 23.1% for those treated with under six cycles of chemotherapy.

This analysis contributes to provide a detailed analysis of clinical prognostic factors in the very elderly DLBCL patient population. Univariate analyses indicated that NCCN-IPI ≥ 5; Age ≥ 83 years; M-CIRS score ≥ 6; Albumin < 35 g/L were predictive poor prognostic factors for both 2-year PFS and 2-year OS. Other variables such as: Male; ABC subtype, Elevated LDH(> 245 IU/L); LVEF ≤ 65%; Renal failure (creatinine > 133 umol/L); ECOG-PS ≥ 2;

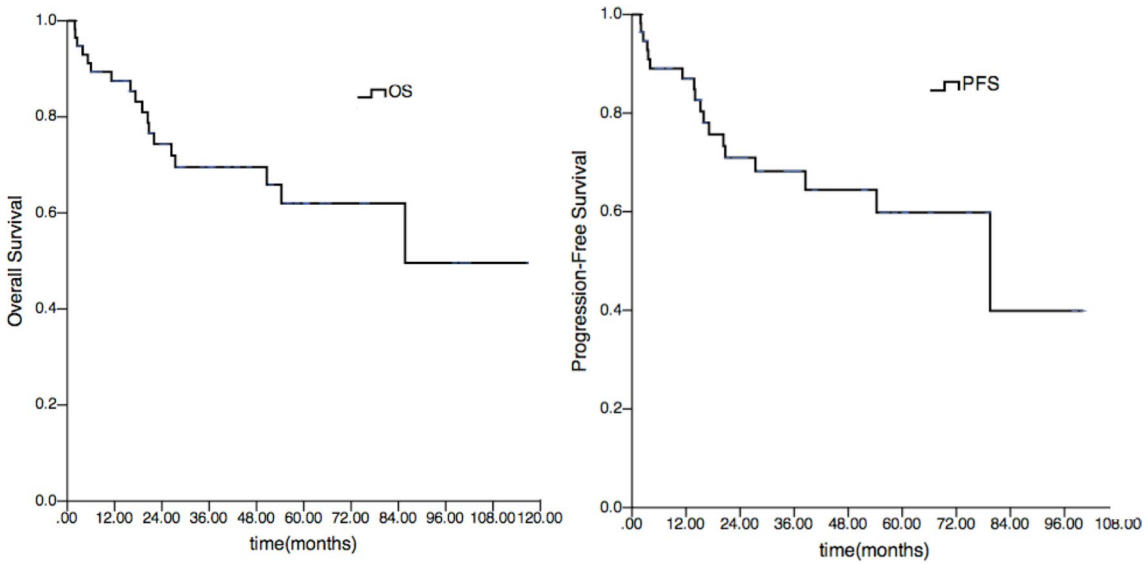

Fig. 2 Kaplan–Meier plots of overall survival (OS) and progression-free survival (PFS) for this cohort

Number of extra-nodal sites ≥ 2; at least six cycles; Anemia (Hgb < 12 g/dL); Presence of B symptoms and Ann Arbor III or IV stage did not have any apparent prognostic significance (Fig. 3, Table 3). An analysis of with Bulky or without was not feasible due to small sample ($n=1$). Noteworthy, in multivariate analyses using the significant prognostic variables from univariate analysis, NCCN-IPI ≥ 5 was the only one factor which had excellent ability to stratify prognosis in patients ≥ 80 years with DLBCL.

In the analysis of this group of very elderly DLBCL patients treated with the reduced-dose R-CHOP regimen, the outcome of those with Age ≥ 83 years; M-CIRS score ≥ 6; Albumin < 35 g/L especially NCCN-IPI ≥ 5 was significantly worse than other patients.

Discussion

To date, our study of treatment patterns and outcomes in DLBCL patients ≥ 80 year is one of the most comprehensive china population-based cohort trials treated with modern chemo-immunotherapy in the real world. With a median

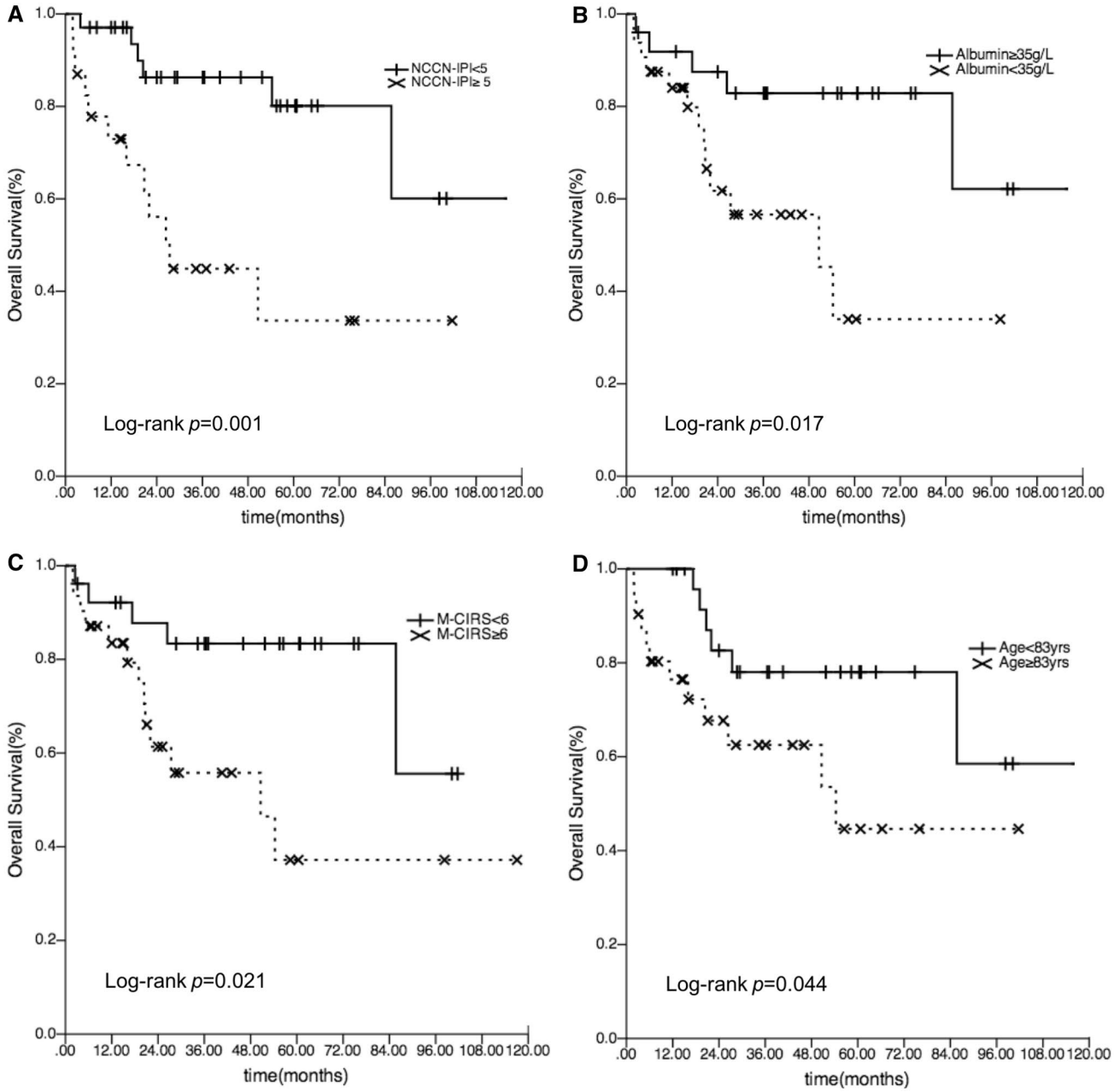

Fig. 3 Univariate analysis of overall survival(OS) in 57 patients according to NCCN-IPI (**a**), Albumin (**b**), M-CIRS (**c**) and Age categories (**d**)

Table 3 Univariate and multivariate analysis of prognostic factors for 2-year overall survival

Factors	Univariate analyses		Multivariate analysis	
	2-year OS (%)	*p* value	Hazard ratio (95% CI)	*p* value
NCCN-IPI ≥ 5	56.1 vs 86.3	0.001	3.722 (1.252–10.966)	0.018
Albumin < 35 g/L	61.7 vs 87.5	0.017	1.080 (0.155–7.518)	0.938
M-CIRS ≥ 6	61.4 vs 87.8	0.021	3.274 (0.507–21.129)	0.212
Age ≥ 83 years	67.7 vs 82.6	0.044	1.787 (0.599–5.328)	0.298
LVEF ≤ 65%	65.3 vs 93.8	0.077	8898	
Elevated LDH	69.1 vs 77.7	0.081		
≥6 cycles	66.7 vs 80.6	0.193		
Renal failure	66.9 vs 78.9	0.208		
No. of extra-nodal sites ≥ 2	72.2 vs 78.0	0.237		
ECOG-PS ≥ 2	66.7 vs 76.8	0.244		
Anemia	69.8 vs 76.7	0.271		
Presence of B-symptoms	70.5 vs 76.2	0.290		
ABC subtype	65.8 vs 80.9	0.388		
Male	72.8 vs 75.1	0.624		
Ann Arbor III or IV	70.7 vs 76.0	0.743		
≥6 cycles	66.7 vs 80.6	0.193		

follow-up period of over 36 months, we provided a detailed analysis of outcome and toxicities from patients with newly diagnosed DLBCL aged ≥ 80 years treated with reduced-dose R-CHOP regimen.

In general, elderly patients have highly heterogeneous characteristics, such as multiple clinical comorbidities, impaired organ function, malnutrition, weakened immune-competence, and limitations to activities of daily living. These conditions seriously affect the metabolism and toxicities of anticancer drugs [29]. The major issue in treating ≥ 80 years patients is to administer the adequate chemotherapy without severe toxic effects and to achieve a long-lasting ORR because the most important point is to define how to adapt treatment to the patient's specificities rather than to apply a unique regimen. Even after the advent of chemo-immunotherapy, the optimal dose intensity for elderly patients with aggressive B-cell lymphomas has been discussed without definitive conclusions. Previous investigations have evaluated reduced intensities of R-CHOP, ranging from 50 to 70% doses of the cytotoxic drugs, for elderly patients with DLBCL [16, 19]. However, an unnecessarily lower dose of key drugs may result in disease progression in potentially curable patients. The trial was designed for ≥ 80-year-old DLBCL patients to apply to the RD R-CHOP regimen which reduced the chemotherapy dose to about 50% of standard dose. In the four cytotoxic drugs of current trial, RDI of Epirubicin was the lowest (average: 82.2%), followed by Prednisone (RDI: 90.0%), Vincristine (RDI: 91.3%), Cyclophosphamide (RDI: 94.0%). Considering that LVEF of 68% patients of the cohort was lower than 65%, and 95% patients had cardiovascular disease, therefore, the reduction of Epirubicin was most commonly seen. It suggested that there were individual differences in the dosage of chemotherapy drugs according to the individual conditions of heart, bone marrow, liver and kidney function, especially in the very elderly patients.

Toxicity profiles of very elderly DLBCL patients were remarkably favorable with an acceptable safety profile in this trial. In the Korean Cancer Study Group LY16-01 trial, more than half of very elderly patients with DLBCL (63.9%) who received full dose of R-CHOP had a high response rate of 92.9% (CR 45.9%) but six patients died due to toxicity (31.6%). In the above study, the main causes of treatment interruption were treatment-related toxicity (45.3%) when giving full dose of R-CHOP consisting of 375 mg/m^2 rituximab, 750 mg/m^2 cyclophosphamides, 50 mg/m^2 adriamycin, and 1.4 mg/m^2 vincristine on day 1, and 100 mg oral prednisone on days 1–5 of each cycle [30]. Similarly, in the LNH03-6B trial, a high treatment-related mortality of 9% was observed in the initial recruitment period, which improved towards the end of the trial [31]. Although high percentages of severe toxicity have been previously reported in the very elderly treated with CHOP [32], the incidence of deaths during chemotherapy in current trial was very low at 3.5%, which is comparable to those reported in retrospective studies in this population (range 7–20%) [33–35], suggesting adequate treatment management in our institution. Remarkably, there is an inevitable trade-off between the ideal dose intensity of R-CHOP and the toxicities confronting elderly patients with DLBCL in practice. As illustrated in our trial, the majority of severe toxicity, including two treatment-related deaths, occurred during the first cycle of therapy. This 'first cycle effect' might be overcome with pre-phase

treatment to improve the tolerance of chemotherapy before administration of a multi-agent therapy [33].

Importantly, the ORR of current trial was just similar to that of LNH03-7B trial (73.7% and 73%, respectively). By contract, the ORR of GELA98.5 study was higher (83%) with the population was younger (median: 80 years). Our observed ORR (73.7%) was much higher than that reported in former phase III trials in the pre-rituximab era illustrating the efficacy of rituximab in DLBCL treatment. Then, the favorable ORR of the current trial was also transformed into the better survival, emphasizing the critical importance of achieving this response outcome. However, compared with the GELA LNH03-7B trial [19], the CR rate of the current trial was less functional. The CR rate of the former trial was 62%, while 26% was in the current trial. Considering that the tumor burden of this cohort was relatively high, advanced disease (Ann Arbor stage III–IV) was seen in 43 (75.5%) of the cases and high-risk group (NCCN-IPI ≥ 4) was in 51 (89.5%) of the patients; this may be one of the primary causes of why the CR rate of current trial was lower than that of LNH 03-7B.

In our study, ≥ 4 cycles RD R-CHOP yielded a median OS of 2.37 years (28.4 mos) among patients ≥ 80 years, just consistent with former studies placing median OS in this population in the range of 2.0–2.5 years [19, 36–38]. With the similar median age and the similar chemotherapy regimens and dosage, the 2-year OS of current study was 74%, which was higher than that of the LNH03-7B trial (59%). Meanwhile, 2-year PFS was higher than that of the LNH03-7B trial group. The reasons may include: the ECOG-PS of this cohort was better than that of the LNH03-7B group (ECOG-PS 4–5 score accounted for 40%), while there was no ECOG-PS 4–5 score group in current cohort. The current results of 3-year PFS 68.2%; 3-year OS 69.5% were slightly worse than outcomes from elderly DLBCL patients treated with six-cycle R-CHOP-14 on RICOVER-60 trial (3-year PFS 73%; 3-year OS 78%) [2, 19]. Of note, our cohort patients' median age(82.5 years) was notably higher than in RICOVER-60 trial (68 years) and LNH03-6B trial (70 years)—to an extent that may be reflected in our dataset. In addition, there were more cases presenting with high IPI score (≥ 3) in our trial than the LNH03-6B trial and RICOVER-60 trial (100% vs 75% vs 43%), which might have contributed to inferior outcome in this trial population. Importantly this study demonstrated that those cases completed six cycles achieved median of 2-year OS: 36.5%, while 23.1% for those treated with under six cycles of chemotherapy. Reduced cycles of the chemotherapy might be one of the reasons for the inferior survival outcome among the very elderly DLBCL patients.

In current trial, several high-risk markers (NCCN-IPI ≥ 5; Age ≥ 83 years; M-CIRS score ≥ 6; Albumin < 35 g/L) were identified in very elderly DLBCL that could potentially refine clinical prognostic models by univariate analyses. Among these factors above, NCCN-IPI ≥ 5 was the only one significant parameter associated with poor outcome by both the univariate and multivariate analysis in current trial. However, the utility of the index needs further evaluation in large-scale, prospective trials. It also elegantly showed that the very elderly patients with high-risk factors especially NCCN-IPI score ≥ 5 could benefit less from immune-chemotherapy. It is useful for the treatment of elderly patients with DLBCL to support risk-oriented personalized therapy.

Older Age and poor performance status had been demonstrated as the two strongest adverse prognostic factors for survival of DLBCL but both should not be the contraindications to the treatment [39, 40]. In current trial, only age showed statistical difference in univariate analysis. It might be that ECOG-PS was just a surrogate for other age-related changes, such as comorbidities and functional decline, but it had little to do with survival outcome.

Studies showed that M-CIRS scores were associated with mortality and hospitalization rates in older patients [40, 41] and the presence of a comorbidity was associated with decreased PFS and OS [42]. Univariate analyses indicated that M-CIRS score ≥ 6 was the predictive poor prognostic factor of PFS and OS in current trial. Thus, a higher prevalence of severity of the complications in very elderly patients could be one of the primary reasons for the failure of treatments for DLBCL.

In particular, recent studies reported that conditions associated with hypoalbuminemia had adverse prognostic impact in elderly patients with DLBCL [12, 19, 43]. However, hypoalbuminemia showed statistical difference in univariate analysis but not in multivariate analyses in this cohort. This might becaused of small group sample and less follow-up time.

However, to optimize R-CHOP treatment for elderly patients with DLBCL, risk-oriented individualized therapy rather than universally attenuated treatment should be applied, because the elderly patients with DLBCL are quite heterogeneous [44]. Based on the current trial above, we hypothesized that very old age (≥ 83 years), hypo-albuminemia (< 35 g/L), and more comorbidities (M-CIRS score ≥ 6) and especially high-risk group (NCCN-IPI ≥ 5) would lead to poor clinical outcomes of ≥ 80-year-old DLBCL patients. High response rate (ORR: 73.7%) was concluded from this trial and the treatment-related toxicity was also reasonable in current trial. Noteworthy, NCCN-IPI ≥ 5 was the only one factor which had excellent ability to stratify prognosis in patients ≥ 80 years with DLBCL in multivariate analyses. We also accept that our limitations in this trial were: there was referral bias in this single-center study, the inherent biases of a non-randomized retrospective study, small group sample and lack of assessing 'quality of life', etc. However, this study is one of the largest analyses of DLBCL patients

older than 80 years and our results reflect the actual clinical practice in China. This may serve as a guide for optimal therapy personalization for very elderly DLBCL patients. It is also noteworthy that better recognition of the biological heterogeneous basis of very elderly patients represents a new pathway for proposing tailored treatment approach. It seems reasonable to advocate an individualized curative treatment for the very elderly patient with DLBCL just like reduced-dose immune-chemotherapy (RD R-CHOP). Personalized treatment algorithms in a given elderly patient with DLBCL should be based on the integration of individual status including stratification of geriatric assessment, risk and prognosis.

Accordingly, over a period of ten years, we demonstrated that reduced-dose R-CHOP therapy was found feasible for the majority of ≥ 80-year-old patients with DLBCL in China. However, the very elderly patients with NCCN-IPI score ≥ 5 would lead to poor outcome. Risk-oriented individualized therapy should be applied. Further well-designed biological-based predictive models will be further assessed and clarify the risk-oriented treatment approaches for the very elderly patients with DLBCL.

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Compliance with ethical standards

Conflicts of interest There is no conflict of interest by any of the authors.

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