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High-Intensity Chemotherapy is Associated with Better Prognosis in Young Patients with High-Risk Diffuse Large B-Cell Lymphoma: A 10-Year Single-Center Retrospective Cohort Study

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Background: Patients <60 years old with high-risk diffuse large B-cell lymphoma (DLBCL) receiving standard RCHOP(E) treatment display high relapse rates. Here, we compared this standard regimen to a high-intensity regimen in terms of recurrence and long-term survival.

Material/Methods: Newly diagnosed DLBCL patients <60 years old who were treated at the Second Hospital Affiliated with Xi'an Jiaotong University between January 2004 and December 2013 (n=198, 18–60 years) were included in the study. The high-intensity group included 107 patients (54.0%) who received >8 courses of chemotherapy (high-dose CHOP, CHOP-E, EPOCH, MAED, MMED, and HyperCVAD). The control group included 91 patients (46.0%) who received 6–8 courses of CHOP-based treatment. Response rate (RR), survival, relapse, and adverse effects were compared.

Results: Baseline characteristics of the patients were similar between the 2 groups. Median follow-up was 64.5 months. RR in the high-intensity and control groups was 88.8% and 84.6% (P=0.387), respectively; 5-year overall survival was 66.4% and 36.3% (P<0.001), respectively; 5-year progression-free survival was 56.1% and 28.6% (P<0.001), respectively; 5-year disease-free survival was 54.2% and 24.2% (P<0.001), respectively; and relapse rate during follow-up was 29.5% and 67.5% (P<0.001), respectively. There were no significant differences in adverse effects between the 2 groups.

Conclusions: High-intensity chemotherapy is associated with better prognosis of patients <60 years old with newly diagnosed high-risk DLBCL.

MeSH Keywords: **Drug Therapy • Drug-Related Side Effects and Adverse Reactions • Lymphoma, B-Cell • Survival Rate**

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Background

Diffuse large B cell lymphoma (DLBCL) is the most common type of adult non-Hodgkin's lymphoma (NHL), accounting for 30–40% of all NHL cases [1,2]. It commonly occurs in middle-aged adults and the elderly [1,2]. Most patients diagnosed in China are 40–50 years old [3,4]. In the United States, DLBCL is the most aggressive of all NHLs, and its incidence has steadily increased by 3–4% each year since the 1990s in all groups of patients [5,6]. An increasing number of patients are stage III–IV at presentation [7]. DLBCL is a heterogeneous disease that is categorized as either germinal center B-cell (GCB type) or non-germinal center B-cell (non-GCB type), according to the Hans classification criteria [8]. According to the age-adjusted International Prognostic Index (aIPI), DLBCL may also be divided into low, low/moderate, moderate/high, and high risk [9].

Although 6–8 courses of CHOP or R-CHOP chemotherapy are standard treatment regimens recommended by NCCN guidelines [10], there is still a high risk of early treatment failure and high relapse rate in young patients with aIPI >1 [11]. Therefore, treatment strategies associated with better prognosis are a clinical necessity. Previous work has suggested that a combination of radiotherapy, reduced chemotherapy intervals, and more intensive regimen could improve the prognosis of high-risk patients [12]. DSHNHL's phase-III trials [13] and Pfreundschuch et al. [14] have shown that an increased number of courses could improve long-term survival, suggesting that compared to 6 courses of chemotherapy, >8 courses could significantly improve the complete response (CR) rate and overall survival (OR) without a significant difference in adverse effects. However, no studies have been conducted to investigate the effect of the specific numbers of courses of treatment.

The objective of this study was to compare the effect of 6–8 vs. >8 courses of chemotherapy in patients <60 years old with newly diagnosed DLBCL and aIPI >1 in terms of recurrence and long-term survival.

Material and Methods

Material

This was a single-center retrospective cohort study of consecutively selected young patients (<60 years old) treated at the Second Hospital Affiliated with Xi'an Jiaotong University between January 2004 and December 2013. These patients were newly diagnosed with DLBCL according to the WHO classification diagnostic criteria for tumors of hematopoietic and lymphoid tissue using histopathology and immunohistochemistry (CD20-positive) [2]. Inclusion criteria were: 1) one or more high-risk factors (elevated serum LDH levels, ECOG of 2–4, and/or

stage III–IV); and 2) high-risk aIPI score (aIPI >1). Exclusion criteria were: 1) progression from indolent lymphoma; 2) relapsed NHL; 3) lymphoma secondary to radiotherapy or chemotherapy; 4) primary NHL of the central nervous system; 5) lymphoma associated with human immunodeficiency virus/acquired immunodeficiency syndrome; 6) tumors after transplantation or other malignant tumors; or 7) heart, liver, and kidney dysfunctions. After application of these criteria, 198 patients were included.

This study was approved by the Ethics Committee of the Second Hospital Affiliated with Xi'an Jiaotong University. Individual consent was waived due to the retrospective nature of the study.

Patient evaluation

All patients underwent a comprehensive assessment before chemotherapy, including bone marrow examination (FISH-NHL and karyotype analysis), electrocardiogram, echocardiogram, chest/abdomen/pelvis computed tomography, B-mode ultrasound examination of superficial lymph nodes, and clinical examination.

Chemotherapy

The experimental group (high-intensity chemotherapy) included 107 patients (54.0%) who received >8 courses of chemotherapy: improved CHOP (CHOP with increased dose intensity), CHOP-E, EPOCH, MAED, MMED, or HyperCVAD. The first choice for all patients was the improved CHOP regimen, followed by CHOP-E, EPOCH, MAED, MMED, and then HyperCVAD. After each course of chemotherapy, routine blood and bone marrow examinations were performed to determine the next course. The interval between 2 courses ranged from 2 to 4 weeks (if white blood cell counts were $<1.0 \times 10^9/L$ or platelets were $<50 \times 10^9/L$ prior to chemotherapy, the chemotherapy was postponed until restoration of blood cell number). Six to eight courses were performed within the first year, followed by 4–5 courses in the second year, and 2–3 courses in the third year; this resulted in a total course number >8 (in most cases, this were 14–16 courses). Outpatient follow-up was conducted every 3 months.

For patients able to afford it, there was a preference for the use of rituximab in combination with chemotherapy (R-CHOP; rituximab: Hoffmann-La Roche Ltd., Basel, Switzerland). Improved CHOP regimen: cyclophosphamide (CTX) 750 mg/m², d1.8; pirarubicin (THP) 30 mg/m², d1.8; vinorelbine (NVB) 25 mg/m², d1.8; and dexamethasone (DXM) 10 mg; d1–8. Improved CHOPE regimen: etoposide (VP-16) 100 mg/m², d1–3 was added to the improved CHOP regimen. MAED regimen: mitoxantrone (MIT) 6 mg/m², d1–3; cytarabine (Ara-c) 100 mg/m², d1–5; VP-16 100 mg/m², d1–3; and DXM 10 mg, d1–5. MMED regimen: MIT 6 mg/m², d1–3; MTX 100 mg/m², d1–3; VP-16 100 mg/m², d1–3;

and DXM 10 mg, d1-5. Improved R-CHOP regimen: same CHOP regimen as above, but the dose of rituximab was 375 mg/m², administered 1 day prior to each course of chemotherapy, for a mean of 3–8 courses (median of 4 courses).

The control group included 91 patients (46.0%) who received 6–8 courses of standard CHOP-based regimens (with or without rituximab).

Radiation therapy

Patients with massive lymphoma (mediastinal mass >1/3 of the pleural diameter or maximum diameter of any lymph node >10 cm on B-mode ultrasound or other examination) or extranodal involvement received local radiotherapy (30–40 Gy).

Symptomatic supportive treatment

During chemotherapy, patients with peripheral blood leucocyte count <2.0×10⁹/L were given subcutaneous G-CSF. If thrombocytopenia was <50×10⁹/L, patients were given TPO (recombinant human thrombopoietin) and hemostasis. If platelets were reduced to <20×10⁹/L or if bleeding tended to occur, patients received infusions of platelet suspension. If hemoglobin was <60 g/L or there was poor cardiopulmonary decompensation or subjective symptoms, patients received RBC suspensions. If grade IV myelosuppression was detected, patients were admitted to a sterile laminar flow ward and were given G-CSF as well as positive and effective antibiotics, fungus infection prevention, immunity enhancement, and supportive treatment.

Assessment of treatment effect

More immediate effects were evaluated after 3 courses of chemotherapy. According to the WHO rating of tumor therapy, assessment was divided into CR, partial response (PR), stable disease (SD), and progressive disease (PD). The response rate (RR) was determined as CR + PR. Additionally, treatment effect was followed over the course of a longer time period; OS, 5-year progression-free survival (PFS), 5-year disease-free survival (DFS), and relapse rate were evaluated during follow-up.

Adverse effects

According to NCI CTC-AE 4.0 version, the toxicity and adverse effects of chemotherapy were divided into 0 (none), I (mild), II (moderate), III (severe), and IV (life-threatening).

Statistical analysis

Statistical analysis was performed using PASW Statistics 20 (IBM Corporation, Armonk, NY, USA). Normality of distribution was evaluated using the Kolmogorov-Smirnov test. Variables

with a normal distribution were compared using the Student's *t*-test, and values are presented as means ± standard deviation. For variables with an abnormal distribution, the Mann-Whitney *U* test was used for comparisons, and values are presented as medians (interquartile range). Categorical variables are presented as frequencies and were analyzed using the chi square or Fisher's exact test, as appropriate. Cox proportional-hazards regression analysis was used for survival data. Two-sided *P*-values ≤0.05 were considered to be statistically significant.

Results

Clinical characteristics of the patients

A total of 198 patients were included: 107 in the high-intensity group (54.0%) and 91 cases (46.0%) in the control group. Clinical characteristics of the patients are presented in Table 1. There were no significant differences in age, gender, extranodal involvement, maximum tumor diameter, bone marrow involvement, B-symptoms, LDH levels, Ann staging, aalPI, or ECOG score between the 2 groups (all *P*>0.05). In addition, there was no difference in the use of rituximab between the 2 groups (28.0% vs. 29.7%, *P*=0.80). Rituximab was not used as maintenance therapy. No patient received autologous blood marrow transplantation.

Treatment effects after 3 courses of chemotherapy

RR of the experimental and control groups was 88.8% (95/107) and 84.6% (77/91) (*P*=0.387), respectively; CR was 75.7% (81/107) and 73.6% (67/91) (*P*=0.738), respectively; and PR was 75.7% (81/107) and 73.6% (67/91) (*P*=0.738), respectively.

The experimental group was divided into 2 subgroups: those who received rituximab treatment and those who did not. RR was 93.3% (28/30) and 87.0% (67/77) (*P*=0.352), respectively, and CR was 83.3% (25/30) and 72.7% (56/77) (*P*=0.251), respectively. The control group was also divided into rituximab and no rituximab subgroups. RR was 85.2% (23/27) and 84.4% (54/64) (*P*=0.922), respectively, and CR was 77.8% (21/27) and 71.9% (46/64) (*P*=0.559), respectively. Regardless of grouping, in patients with non-GCB, rituximab could significantly improve the efficacy of chemotherapy (*P*=0.045, *P*=0.041).

Treatment effects at follow-up

As of September 30, 2014, follow-up times ranged from 9 to 103 months, with a median follow-up of 64.5 months. The number of courses in the high-intensity and control groups was 9–16 (median of 14) and 6–8 (median of 8), respectively.

Table 1. Clinical characteristics of the patients.

	High-intensity group N=107 (54.0%)		Control group N=91 (46.0%)		P-value
Age (years), median (range)	53	(18–60)	55	(18–60)	0.634
Gender, n (%)					0.954
Male	56	(52.3)	48	(52.8)	
Female	51	(47.7)	43	(47.3)	
Number of extranodal sites, median (range)	1	(0–4)	1	(0–4)	0.733
Extranodal involvement, n (%)					0.858
Yes	73	(68.2)	61	(67.0)	
No	34	(31.8)	30	(33.0)	
B-symptoms, n (%)					0.822
Yes	71	(66.36)	59	(64.84)	
No	36	(33.64)	32	(35.16)	
Immunophenotype, n (%)					0.983
GCB	41	(38.3)	35	(38.5)	
Non-GCB	66	(61.7)	56	(61.5)	
Performance status, n (%)					0.728
ECOG 0–1	74	(69.2)	65	(71.4)	
ECOG 2–4	33	(30.8)	26	(28.6)	
LDH >UNV, n (%)					0.529
Yes	103	(96.3)	89	(97.8)	
No	4	(3.7)	2	(2.2)	
Stage, n (%)					0.914
I–II	31	(29.0)	27	(29.7)	
III–IV	76	(71.0)	64	(70.3)	
aaIPI, n (%)					0.914
2	83	(77.6)	70	(76.9)	
3	24	(22.4)	21	(23.1)	
Maximum tumor diameter, n (%)					0.800
≥10 cm	30	(28.0)	27	(29.7)	
<10 cm	77	(72.0)	64	(70.3)	
BM infiltration, n (%)					0.808
Yes	22	(20.6)	20	(22.0)	
No	85	(79.4)	71	(78.0)	
Prophylactic CNS treatment, n (%)					0.989
Yes	34	(31.8)	29	(31.9)	
No	73	(68.2)	62	(68.1)	
Radiotherapy, n (%)					0.727
Yes	39	(36.5)	31	(34.1)	
No	68	(63.6)	60	(65.9)	
Rituximab					0.800
Yes	30	(28.0)	27	(29.7)	
No	77	(72.0)	64	(70.3)	

ECOG – Eastern Cooperative Oncology Group; BM – bone marrow; LDH – lactate dehydrogenase; aaIPI – age-adjusted international prognostic index; CNS – central nervous system.

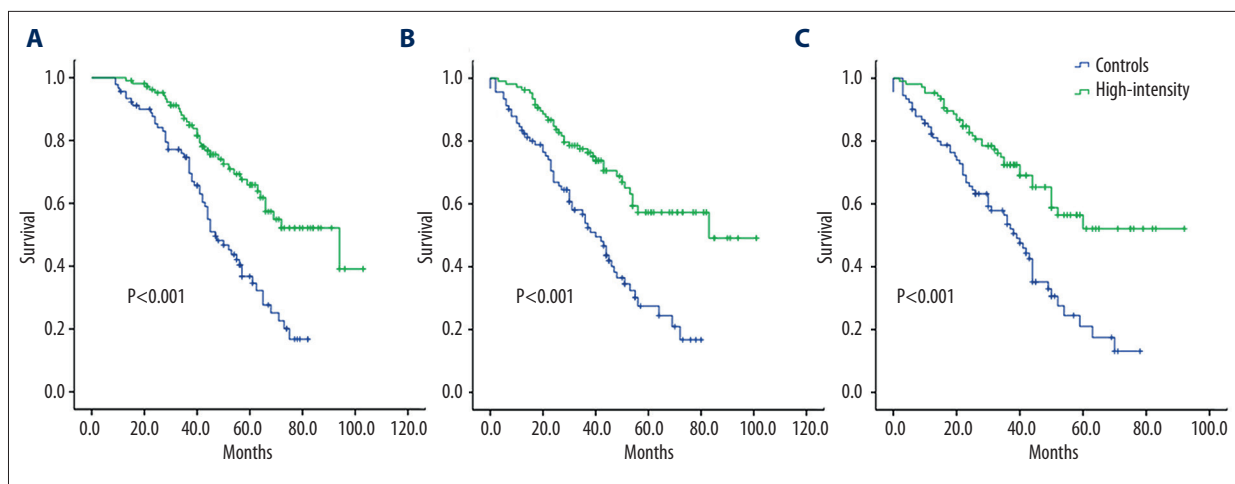


Figure 1. Survival of the control and high-intensity groups. (A) Overall survival. (B) Progression-free survival. (C) Disease-free survival.

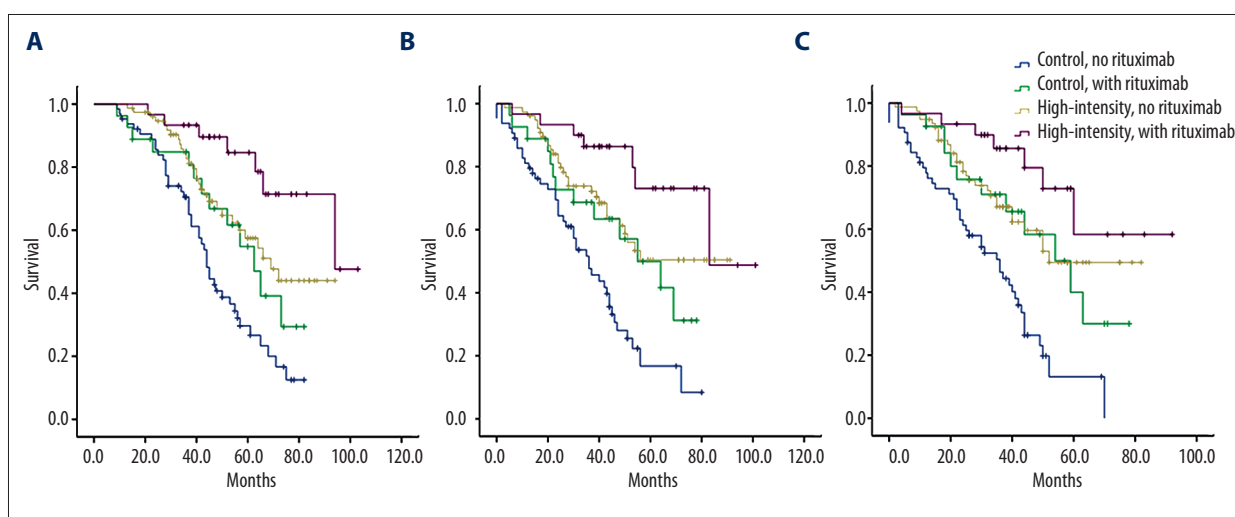


Figure 2. Survival according to rituximab combination. (A) Overall survival. (B) Progression-free survival. (C) Disease-free survival.

The 5-year OS in the high-intensity and control groups was 66.4% and 36.3% ($P < 0.001$), respectively; the 5-year PFS was 56.1% and 28.6% ($P < 0.001$), respectively; the 5-year DFS was 54.2% and 24.2% ($P < 0.001$), respectively; and the relapse rate during follow-up was 29.5% and 67.5% ($P < 0.001$), respectively (Figure 1).

In the high-intensity group, comparing the rituximab vs. no rituximab subgroups, the 5-year OS was 86.7% (26/30) and 58.4% (45/77) ($P = 0.006$), respectively; the 5-year PFS was 70.0% (21/30) and 50.7% (39/77) ($P = 0.07$), respectively; and the relapse rate during follow-up was 21.4% (6/28) and 32.8% (22/67) ($P = 0.266$), respectively. In the control group, the 5-year OS was 51.9% and 29.7% ($P = 0.045$), respectively; the 5-year PFS was 48.2% and 20.3% ($P = 0.007$), respectively; and the relapse rate during follow-up was 43.5% (10/23) and 77.8% (42/54) ($P = 0.003$), respectively (Figure 2).

For the GCB and non-GCB subgroups, the 5-year OS was 67.1% and 43.4% ($P = 0.001$), respectively, and the 5-year PFS was 55.3% and 36.1% ($P = 0.008$), respectively. In the GCB subgroup 25.0% (19/76) of patients received rituximab, and 31.2% (38/122) of patients in the non-GCB subgroup received rituximab. The OS and PFS of the chemotherapy and rituximab combination were better than chemotherapy alone in both GCB and non-GCB subgroups (both $P < 0.001$) (Figure 3).

Multivariate analysis

A multivariate analysis was performed to analyze the clinical characteristics associated with survival. Results showed that the total number of courses of chemotherapy, chemotherapy regimens, aalPI, and immunological type were independent prognostic indicators of OS, PFS, and DFS (Table 2).

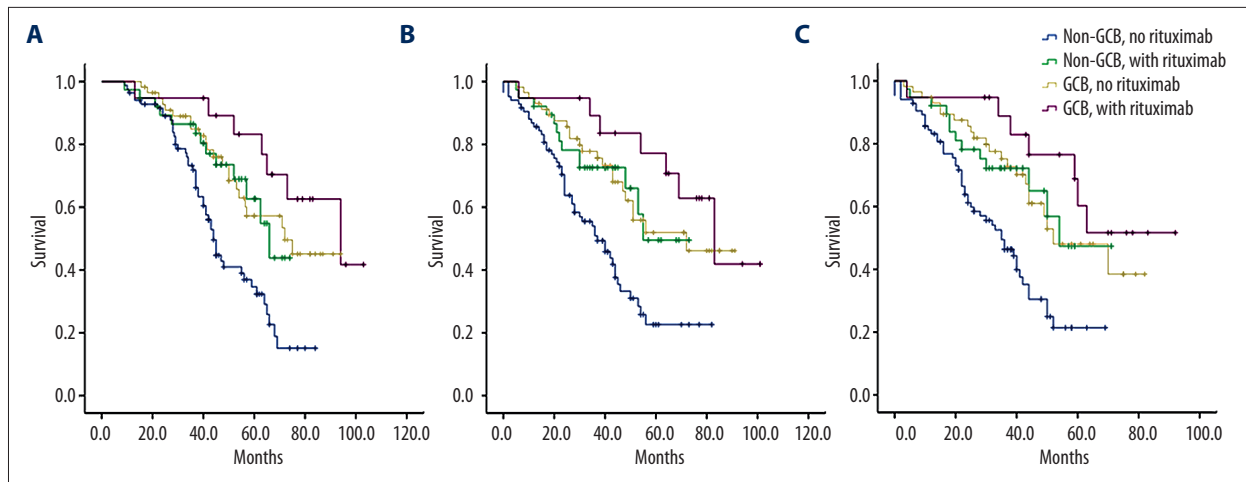


Figure 3. Survival according to GCB and Non-GCB subtypes and to rituximab combination. (A) Overall survival. (B) Progression-free survival. (C) Disease-free survival.

Table 2. Multivariate analysis of the effects of high-intensity regimens on OS, PFS, and DFS in DLBCL.

Influencing factor	OS			PFS			DFS		
	P-value	RR	95%CI	P-value	RR	95%CI	P-value	RR	95%CI
Total number of chemotherapy course	<0.001	0.846	(0.788, 0.909)	<0.001	0.829	(0.770, 0.892)	<0.001	0.829	(0.770, 0.893)
Chemotherapy regimen	0.020	0.546	(0.328, 0.910)	0.025	0.557	(0.334, 0.928)	0.025	0.558	(0.335, 0.930)
aalPI	0.007	1.840	(1.184, 2.859)	0.001	2.200	(1.400, 3.459)	0.001	2.174	(1.382, 3.419)
Immunological type	<0.001	0.422	(0.267, 0.667)	<0.001	0.394	(0.248, 0.625)	<0.001	0.390	(0.245, 0.619)

OS – overall survival; DFS – disease-free survival; PFS – progression-free survival; RR – relative risk; 95%CI – 95% confidence interval; aalPI – age-adjusted international prognostic index.

Safety and toxic adverse effects

In the high-intensity group, the increased courses of chemotherapy and increased dose intensity resulted in increased infusion of blood products, antibiotics, and G-CSF (Table 3). However, all toxicities and adverse effects were controllable, and the main observation indexes (including chemotherapy-related mortality) were similar between the 2 groups. All doses of chemotherapy drugs were within the allowed ranges.

In the high-intensity and control groups, 5 and 3 patients with chronic hepatitis B received rituximab, respectively. After receiving strengthened autoantibodies, reactivation incidence of hepatitis B virus was 40.0% (2/5) and 33.3% (1/3), respectively.

Discussion

The objective of the present study was to compare 6–8 vs. >8 courses of chemotherapy in patients <60 years old who were

newly diagnosed with DLBCL and who had aalPI >1. Outcomes were evaluated in terms of recurrence and long-term survival. Results showed that baseline characteristics of the patients were similar between the 2 groups. Median follow-up was 64.5 months. There was no difference in RR between the 2 groups. Five-year overall survival, 5-year progression-free survival, 5-year disease-free survival, and relapse rates were better in the high-intensity group. There were no significant differences in adverse effects between the 2 groups.

There are no uniform regimens that are recommended in young patients with DLBCL and aalPI >1 [10,11]. Despite this, 6–8 courses of RCHOP/RCHOPE chemotherapy is standard, but relapse rates are high, at approximately 37–47% at 3 years [13,14]. For patients with contraindications to rituximab or for patients unable to afford rituximab, alternative therapies are necessary. The DSHNHL trial confirmed that the number of chemotherapy courses can affect the efficacy and long-term survival of patients with DLBCL [13]. However, no studies have been conducted to clarify whether there are significant

Table 3. Grades III/IV toxic side effects and therapeutic intervention measures.

	High-intensity group	Control group	P-value
III/IV side effects			
Leukopenia	80.4%	62.6%	0.070
Anemia	33.6%	22.0%	0.069
Thrombocytopenia	32.7%	19.8%	0.062
Neutrocytopenia	71.0%	53.8%	0.060
Nausea and vomiting	16.8%	9.9%	0.157
Abnormal liver function	0.2%	0.0%	0.335
Abnormal renal function	0.0%	0.0%	
Lipsotrichia	1.9%	1.1%	0.658
Cardiotoxicity	0.0%	0.0%	
Peripheral neuritis	0.0%	0.0%	
Mouth ulcers	14.9%	6.6%	0.062
Persistent fever and neutropenia	4.7%	3.3%	0.624
Allergy	2.8%	2.2%	0.787
Therapeutic intervention measures			
Erythrocyte transfusion			
Single patient	44.8%	32.9%	0.088
Single course	28.0%	17.6%	0.083
Platelet transfusion			
Single patient	22.4%	15.4%	0.210
Single course	9.3%	4.4%	0.176
Antibiotic			
Single patient	65.4%	49.5%	0.070
Single course	25.2%	18.7%	0.269

efficacy differences between 6–8 and >8 courses of chemotherapy, as well as how to select an appropriate number of courses to minimize the relapse rate.

The present study suggests that a high-intensity regimen may achieve long-term effects in young patients with aggressive disease that are similar to those obtained by regimens recommended by NCCN guidelines [10]. In addition, the use of rituximab seemed to improve survival. However, some differences were not statistically significant, which may be due to the small number of patients in some subgroups.

In 2010, the Danish Lymphoma Study Group retrospectively analyzed 159 young patients with high-risk DLBCL, in which all patients received 6–8 courses of R-CHOP(E)-14. Their results have shown that the 4-year OS of the R-CHOPE-14 and R-CHOP-14 groups was 75% and 62%, respectively, and that

the 4-year PFS was 70% and 58%, respectively [15]. In the present study, the 5-year OS of the >8 courses of rituximab group was 86.7%, which was significantly higher than the 6–8 courses of R-CHOP(E) regimen observed in the Danish study. However, the PFS results were comparable. In the present study, the 5-year OS and PFS of the high-intensity group without rituximab was 58.4% and 50.7%, respectively, which were comparable to those of the 6–8 courses of R-CHOP-14 regimen in the Danish study. These results strongly suggest that improved regimens with increased courses and dose intensity are superior to conventional CHOP (E), and that they can significantly improve long-term efficacy. These observations are also supported by the DSHNHL's phase III clinical trials [13] and results from Adde et al. [16,17].

Compared to traditional CHOP regimens, the improved CHOP regimen used at our center uses THP instead of

Adriamycin (ADM), NVB instead of leucovorin, and intravenous infusion of DXM instead of oral administration of prednisone. This approach could lead to some advantages. First, THP is a newly synthesized anthracycline antitumor antibiotic [18,19]. Its primary mechanism of action involves entering the cell nucleus, binding to DNA, inhibiting DNA polymerase, interfering with mitosis, and eventually killing cells. Compared to ADM, the structural changes in THP increase its liposolubility, which enables it to quickly enter cells, while diffusing out slowly, resulting in a high intracellular concentration and improved antitumor activity [20]. Chemotherapy regimens containing THP or ADM used in patients with NHL resulted in cardiotoxicity rates of 1.5% and 14.2%, respectively [21]. Studies have shown that irreversible cardiotoxicity occurred with a maximum cumulative dose of 450 mg/m² of ADM, while the maximum cumulative dose of THP was 1500 mg/m² [22]. Therefore, THP might be more suitable for some patients, especially elderly patients. Secondly, NVB is a semi-synthetic vinca alkaloid compound targeting microtubules [23]. Compared to other vinca alkaloid drugs, NVB presents poor affinity to axons, and only a high concentration can affect the axonal microtubules, resulting in relatively low neurotoxicity [24]. In addition, NVB's monotherapy efficiency is high in patients who had failures with other regimens [25,26]. Thirdly, DXM is a long-lasting glucocorticoid that is a cell cycle-nonspecific agent. It has lymphocytolysis effects on lymphoma, prompts adipolysis of lymphocytes, and prevents re-esterification of fatty acids, leading to fatty acid accumulation in cells, as well as karyoclasia and cytoclasis [27]. Compared to prednisone, DXM can more effectively reduce CNS infiltration or recurrence and reduce the adverse effects of chemotherapy [28].

In this study, the high-intensity regimens resulted in better outcomes compared to conventional regimens. This may be due to a number of reasons. First, drug doses were increased during remission induction, and the administration was focused on the 1st and 8th days. Second, these drugs had synergistic effects, which enhanced efficacy and prevented drug resistance. Adverse effects were mild and tolerable. In particular, cardiovascular toxicity of THP and the neurotoxic effect of NVB were milder, which improved the patients' quality of life and was helpful for consequent consolidating and strengthening treatment. Third, in the consolidating and strengthening stages, we used alternate chemotherapy regimens of CHOPE, MAED, MMED, and TAED that reduced drug resistance of tumor cells. Fourth, in cases of severe drops in patients' immunity, patients were admitted in a sterile laminar flow ward as

soon as possible to strengthen supportive therapy and to avoid chemotherapy-related death. Finally, courses of therapy were extended to the limits of patients' tolerance. Taken together, these factors may be responsible for the favorable outcomes observed in the present study.

Due to tolerance issues, many clinicians believe that prolonging chemotherapy courses should be avoided in patients with ECOG of 2-4 and severe complications. However, in the present study, patients were at high risk of relapse and complications, and there were no differences in the clinical characteristics of the 2 groups. Moreover, severe complications were not common.

In this study, the proportion of non-GCB cases was higher than that of GCB cases. Five-year survival rates suggested that the prognosis of the GCB type might be superior to that of the non-GCB type. These results are supported by previous studies showing that the survival of GCB type had obvious advantages over the non-GCB type [13,14].

The present study is not without limitations. Indeed, the sample size was small and follow-up duration was short. In addition, the inherent limitations of retrospective studies limit the immediate applicability of these results. Only some of the patients in this study were tested for cytogenetic and karyotype alterations. Therefore, these results could not be used in this study, but future studies will aim at assessing the associations between prognosis and FISH and karyotype results. Further randomized controlled studies with larger sample sizes are necessary to clarify whether this therapy regimen can be considered as an initially optimized regimen in young patients with high-risk DLBCL.

Conclusions

In conclusion, the present study suggests that young patients with high-risk, newly diagnosed DLBCL could benefit from >8 courses of chemotherapy. OS, PFS, DFS, and relapse rates were better in the >8 courses of chemotherapy compared with 6-8 courses, with good tolerance. Further prospective trials to test these high-intensity regimens are necessary.

Conflict of interest

The authors declare that they have no conflicts of interest.

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