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Research Article

Prognosis and Microbiome Analysis of First-Line Consolidation with Autologous Hematopoietic Stem Cell Transplantation in Intermediate-to-High-Risk Diffuse Large B-Cell Lymphoma

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Abstract

Objective: To evaluate the safety and efficacy of first-line consolidation with autologous hematopoietic stem cell transplantation (AHSCT) in intermediate-to-high-risk diffuse large B-cell lymphoma (DLBCL). **Methods:** A total of 70 newly diagnosed, intermediate-to-high-risk DLBCL patients who achieved complete response (CR) after rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy at the Department of Hematologic Oncology, Cancer Hospital of the Chinese Academy of Medical Sciences, Shenzhen Hospital between June 2018 and December 2023 were retrospectively analyzed. Patients who received sequential AHSCT as first-line consolidation therapy were included in the transplantation group (n = 35), whereas those who did not receive sequential AHSCT consolidation during the same period served as the control group (n = 35). The clinical efficacy and safety were compared between the two groups. **Results:** As of the final follow-up on December 31, 2025, the median follow-up time was 59 (51–63) months in the transplantation group and 62 (45–68) months in the control group. The 5-year disease-free survival (DFS) rate in the transplantation group was significantly higher than that in the control group (66.7% vs. 44.7%, P = 0.012); however, no statistically significant difference was observed in the 5-year overall survival (OS) rate (70.6% vs. 62.5%, P = 0.42). Cox multivariate analysis indicated that non-sequential AHSCT consolidation therapy, double expression, and bone marrow involvement (BMI) were independent adverse prognostic factors for DFS (HR = 5.583, 95%CI = 2.199–14.175, P < 0.001; HR = 3.240, 95% CI = 1.492–7.037, P = 0.003; HR

= 6.225, 95% CI = 2.535–15.282, P < 0.001, respectively). In 15 transplanted patients treated with the oropharyngeal probiotic BP-OM1, salivary levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were significantly elevated compared to the controls. No transplant-related mortality occurred in the transplantation group, and bacterial, fungal, and viral infections occurring during the peri-transplantation period were completely cured after symptomatic treatment. **Conclusion:** For patients with newly diagnosed intermediate-to-high-risk DLBCL who achieve CR after R-CHOP chemotherapy, sequential first-line consolidation with AHSCT can significantly improve the DFS rate with favorable safety and efficacy.

Key words: Autologous hematopoietic stem cell transplantation (AHSCT); intermediate-to-high-risk; diffuse large B-cell lymphoma (DLBCL); Safety; Efficacy.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is a group of highly heterogeneous tumors and represents the most common type of non-Hodgkin lymphoma (NHL), accounting for approximately 30% of the pathological subtypes of adult NHL (1-3). DLBCL carries the heaviest global burden of lymphoma-related mortality (4). Its clinical manifestations typically include progressive lymphadenopathy or extranodal organ involvement. Active treatment is mandatory for both early- and advanced-stage DLBCL, and most patients are already at an advanced stage at the time of diagnosis. Rituximab is a monoclonal antibody targeting cluster of differentiation 20 (CD20). The R-CHOP regimen (comprising rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) serves as the standard first-line chemotherapy for newly diagnosed DLBCL, yielding a 5-year survival rate of approximately 50%–70% (5,6).

Although the R-CHOP regimen has tremendously improved the survival rate of patients with DLBCL, approximately 20% of patients eventually develop refractory disease, and 30%–40% experience relapse (7,8). For patients with relapsed or refractory disease, although salvage strategies such as programmed death-1 (PD-1) inhibitors, targeted therapies combined with chemotherapy, or later-line chemotherapy regimens can be subsequently administered (9-11), their clinical efficacy remains unsatisfactory. To reduce disease progression and recurrence, prolong patient survival, and improve prognosis, it is highly necessary to explore effective consolidation strategies for DLBCL patients who achieve complete response (CR) after first-line chemotherapy. With the emergence and maturation of autologous hematopoietic stem cell transplantation (AHSCT), it has been widely applied in the treatment of DLBCL. AHSCT plays a critical role in both first-line consolidation for DLBCL and salvage therapy for relapsed or refractory lymphoma, potentially prolonging patients' progression-free survival (PFS) and overall survival (OS) (12-15). However, some international studies have proposed alternative perspectives regarding consolidation strategies for DLBCL patients, suggesting that AHSCT might not be the optimal frontline consolidation regimen (16,17).

To date, whether AHSCT can serve as a standard first-line consolidation strategy for DLBCL patients requires further validation, and additional clinical trials are urgently needed to analyze the feasibility of this approach. Since June 2018, our center has implemented AHSCT as a first-line consolidation therapy for newly diagnosed, intermediate-to-high-risk DLBCL patients who achieved CR after R-CHOP chemotherapy. Herein, we analyze the clinical data of 35 patients who received sequential AHSCT as first-line consolidation, aiming to explore the clinical efficacy and safety of AHSCT in this setting.

2. Materials and Methods

2.1 General Data

A retrospective analysis was performed on newly diagnosed, intermediate-to-high-risk (International Prognostic Index [IPI] score ≥ 3) DLBCL patients who achieved CR after prior R-CHOP chemotherapy at the Department of Hematologic Oncology, Cancer Hospital, Chinese Academy of Medical Sciences, Shenzhen Hospital between June 2018 and December 2023. Patients were divided into a transplantation group and a control group based on whether they received sequential AHSCT as first-line consolidation therapy. All patients were diagnosed with DLBCL by histopathological biopsy and immunohistochemical staining in the Department of Pathology at our hospital. Bone marrow aspiration and biopsy were performed in all patients to determine bone marrow involvement (BMI). The expression of MYC, Bcl-2, and Bcl-6 in tumor tissues was evaluated; double-expression lymphoma (DEL) was defined as the overexpression of MYC and Bcl-2/Bcl-6 proteins, with cut-off values set at MYC ⩾ 40%, Bcl-2 ⩾ 50%, and Bcl-6 ⩾ 30%. Ann Arbor staging and Eastern Cooperative Oncology Group (ECOG) performance status scores were determined for all patients at initial diagnosis, and risk stratification was performed according to the IPI scoring criteria (18). None of the patients had major organ dysfunction. Contrast-enhanced computed tomography (CT) or positron emission tomography-computed tomography (PET-CT) was regularly performed during treatment to evaluate clinical response.

2.2 Pre-mobilization Treatment Regimen

The transplantation group received sequential AHSCT as first-line consolidation therapy after R-CHOP chemotherapy, whereas the control group did not receive sequential AHSCT consolidation after chemotherapy. The total number of chemotherapy cycles before transplantation in the transplantation group was 239, with a median of 7 cycles (range: 6–7 cycles). The total number of chemotherapy cycles in the control group was 232, with a median of 6 cycles (range: 6–7 cycles). No statistically significant difference was observed in the total number of chemotherapy cycles between the two groups (P=0.196). Peripheral blood stem cell (PBSC) collection was performed after four cycles of R-CHOP chemotherapy. The R-CHOP regimen consisted of rituximab 375 mg/m² on day 0. The CHOP regimen included cyclophosphamide (CTX) 750 mg/m², doxorubicin (ADM) 50 mg/m² or liposomal doxorubicin 30 mg/m², and vincristine (VCR) 1.4 mg/m² on day 1, combined with prednisone (PDN) 60 mg/m² on days 1–5. Routine blood counts, liver and kidney function, electrolytes, myocardial enzymes, and electrocardiograms were regularly monitored during the treatment period.

2.3 Hematopoietic Stem Cell Mobilization

Before mobilization, all patients in the transplantation group underwent comprehensive screening for infectious indicators, including routine blood, urine, and stool tests, procalcitonin (PCT), C-reactive protein (CRP), tuberculin skin test, fungal galactomannan (GM) assay, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), syphilis-specific antibody, Epstein-Barr virus (EBV), and cytomegalovirus (CMV). Chest CT and abdominal imaging were also completed to exclude occult infectious foci. Prior to transplantation, imaging evaluations confirmed that all patients in the transplantation group had achieved CR, with no active bacterial, fungal, or viral infections. Hematopoietic, cardiopulmonary, hepatic, and renal functions had returned to normal in all patients before mobilization. The mobilization strategy utilized chemotherapeutic agents combined with granulocyte colony-stimulating factor (G-CSF). Among them, 22 patients received single-agent CTX chemotherapy, and 13 patients received the EAC regimen (comprising etoposide, CTX, and cytarabine). G-CSF was administered subcutaneously at a dose of 5–10μg/(kg·d) for 3–5

consecutive days, initiated at the nadir of peripheral white blood cell counts. PBSC collection was performed when the peripheral blood CD34+ cell count exceeded 20 cells/μL.

2.4 Conditioning Regimen

The conditioning regimens consisted of either the BUCY regimen or the BEAM regimen, administered to 24 and 11 patients, respectively. The specific protocols were as follows: BUCY regimen: Busulfan 3.2 mg/(kg·d) from day -6 to day -4, and CTX 50 mg/(kg·d) from day -3 to day -2. BEAM regimen: Carmustine 300 mg/(m²·d) on day -8, etoposide 200 mg/(m²·d) from day -7 to day -4, cytarabine 200 mg/(m²·d) from day -7 to day -4, and melphalan 100–140 mg/(m²·d) on day -2. To reduce the incidence of infection post-AHSCT, 15 transplanted patients routinely received the oropharyngeal probiotic BP-OM1 starting from the initiation of conditioning until 1 month post-transplantation. Specifically, patients were allowed the probiotic lozenge to dissolve completely in the mouth (approximately 4–5 minutes) after brushing their teeth in the morning and evening, ensuring no chewing or direct swallowing of the lozenge. Patients were instructed to avoid eating or drinking within 2 hours after administration. Additionally, salivary cytokine testing was performed in these 15 patients before and after probiotic use, involving sample preparation, polymerase chain reaction (PCR) amplification, electrophoresis detection, and subsequent data analysis.

2.5 Stem Cell Infusion and Supportive Care

Following the completion of the conditioning regimen, thawed autologous hematopoietic stem cells were infused, accompanied by enhanced supportive care. Valacyclovir was administered to prevent viral infections, fluconazole for fungal prophylaxis, and sulfamethoxazole/trimethoprim to prevent Pneumocystis jirovecii pneumonia. Patient temperature, complete blood count, urinalysis, and biochemical indicators were closely monitored daily. Packed red blood cell transfusions were administered when hemoglobin fell below 70 g/L, and platelet transfusions were given when the platelet count dropped below 20×10^9/L.

2.6 Monitoring of Infectious Events During Transplantation

Infectious events occurring in the transplantation group from the start of stem cell mobilization to hematopoietic reconstitution after transplantation were documented in detail. In this study, infectious events were categorized into three types: bacterial, fungal, and viral infections. Bacterial infections included respiratory tract, gastrointestinal tract, bloodstream, skin and soft tissue, and urinary tract infections, with pathogenic evidence serving as the diagnostic criteria. Fungal infections included invasive and superficial fungal infections, diagnosed based on a positive fungal GM assay, typical mycotic lesions on imaging, or positive pathogenic cultures. Viral infections were comprehensively evaluated based on clinical manifestations, imaging changes, and microbiological testing, with pathogenic evidence required for a definitive diagnosis. All infectious cases were reviewed and confirmed by two or more attending physicians in the department, and the onset time, site of infection, pathogen type, therapeutic regimen, duration of infection control, and clinical outcomes were recorded in detail.

2.7 Efficacy Evaluation and Follow-up

Clinical response was evaluated via contrast-enhanced CT or PET-CT imaging according to the 2014 Lugano classification for lymphoma (19), categorized into CR, partial response (PR), stable disease (SD), and progressive disease (PD). Adverse drug reactions were graded from I to IV using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Follow-up was conducted by reviewing inpatient records, outpatient charts, or via telephone interviews, with a data cut-off date of December 31, 2025. Contrast-enhanced CT or PET-CT was

performed every 3–6 months during the first 2 years, and contrast-enhanced CT every 6 months or PET-CT every 12 months during years 3–5. The primary endpoint was disease-free survival (DFS), defined as the time from the completion of transplantation (transplantation group) or completion of chemotherapy (control group) to the first documentation of disease recurrence, progression, or death from any cause. The secondary endpoint was OS, defined as the time from randomization to death from any cause.

2.8 Statistical Methods

Statistical analyses were performed using Statistical Product and Service Solutions (SPSS) software, version 25.0. Intergroup comparisons of quantitative data were analyzed using the independent two-sample t-test or the rank-sum test. Categorical data were compared using the Chi-square ($\chi 2$) test. Survival analysis was performed using the Kaplan-Meier method to construct survival curves, and the log-rank test was used to compare DFS and OS between the transplantation and control groups. Univariate analysis was performed using the Cox proportional hazards regression model, and variables with statistical significance in the univariate analysis were subsequently entered into a multivariate Cox regression analysis. A value of $P < 0.05$ was considered statistically significant.

3. Results

3.1 Patient Clinical Characteristics

A total of 74 newly diagnosed, intermediate-to-high-risk DLBCL patients who achieved CR after chemotherapy were initially screened in this study. Among them, four patients were excluded based on the inclusion and exclusion criteria: two patients developed secondary central nervous system (CNS) tumors, and two refused follow-up. Ultimately, 70 patients were included in the final analysis. Of these 70 patients, 35 underwent sequential AHSCT as first-line consolidation therapy after chemotherapy (transplantation group, n = 35), and 35 did not receive sequential AHSCT consolidation after chemotherapy (control group, n = 35). In the transplantation group, there were 23 males (65.7%) and 12 females (34.3%), with a median age of 51 years (range: 44–58 years). In the control group, there were 20 males (57.1%) and 15 females (42.9%), with a median age of 52 years (range: 42–66 years). Comparison of the clinical characteristics between the two groups revealed a statistically significant difference in the presence of extranodal involvement ($P = 0.002$). Howeverr, no statistically significant differences were observed in terms of sex, age, cell of origin (COO), Ann Arbor stage, IPI score, Ki-67 index, double-expression status, bone marrow involvement (BMI), tumor size, or B symptoms (all $P > 0.05$; Table 1)

3.2 Hematopoietic Reconstitution

In the 35 patients of the transplantation group, the median number of infused CD34+ cells was 4.62×106/kg (range: 1.88×106/kg to 17.64×106/kg), and the median number of mononuclear cells (MNCs) was 7.81×108/kg (range: 4.28×108/kg to 15.36×108/kg). No severe complications occurred in any of the transplanted patients during the transplantation period, and all patients achieved successful hematopoietic reconstitution. The median time to neutrophil engraftment was 11.6 days (range: 8–17 days), and the median time to platelet engraftment was 15.8 days (range: 11–22 days).

3.3 Electrophoresis Results After Probiotic Administration in the Transplantation Group

Among the 35 patients in the transplantation group, 15 initiated probiotic therapy one month prior to transplantation. Salivary cytokine testing was performed for all 15 patients after probiotic administration using electrophoresis of qPCR products. The experimental electrophoresis results are presented in Figures 1A–1F. The results demonstrated that salivary levels of IL-6 and TNF-α were significantly elevated in patients after receiving

the oropharyngeal probiotic BP-OM1 intervention compared with the controls. This suggests that BP-OM1 intervention may help alleviate the levels of respiratory tract inflammation in DLBCL patients undergoing transplantation.

Table 1. General information of the transplant group and control group (cases, %).

Patient Characteristics	Treatment group (n=35)	Control group (n=35)	*P* value
Gender			0.461
Male	23(65.7%)	20(57.1%)	
Female	12(34.3%)	15(42.9%)	
Age (years)			0.122
60 years old	27(77.1%)	21(60%)	
≥60 years old	8(22.9%)	14(40%)	
Age (years)	51(44-58)	52(42-66)	0.176
Cell origin			0.743
Non-GCB	29 (82.9%)	30(85.7%)	
GCB	6 (17.1%)	5(14.3%)	
Ann Arbor stage			0.074
I-II	2(5.7%)	7(20%)	
III-IV	33(94.3%)	28(80%)	
IPI score			0.597
3	24(68.6%)	26(74.3%)	
≥4	11(31.4%)	9(25.7%)	
Ki-67			0.356
< 70%	8(22.9%)	5(14.3%)	
≥70%	27(77.1%)	30(85.7%)	
Invasive site			0.002
Lymph gland	9(25.6%)	22(62.9%)	
Extranodal invasion	26(74.3%)	13(37.1%)	
Double expression			0.445
No	22(62.9%)	25(71.4%)	
Yes	13(37.1%)	10(28.6%)	
Bone marrow invasion			0.55
No	27(77.1%)	29(82.9%)	
Yes	8(22.9%)	6(17.1%)	
Large lump (⩾7.5 cm)			0.057
No	26(74.3%)	32(91.4%)	
Yes	9(25.7%)	3(8.6%)	
B Symptom			0.403
No	25(71.4%)	28(80%)	
Yes	10(28.6%)	7(20%)	

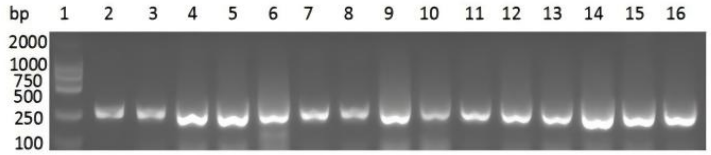


Fig.1A Electropherogram of qPCR products

（1.DL2000；2. I123/h-actinβ；3.I127/h-actinβ；4.I130/h-actinβ；5.I131/h-actinβ；6.I135/h-actinβ；7.I124/h-actinβ；8.I125/h-actinβ；9.I137/h-actinβ；10.I138/h-actinβ；11.I128/h-actinβ；12.I129/h-actinβ；13.I134/h-actinβ；14.I136/h-actinβ；15.I132/h-actinβ；16.I133/h-actinβ）



Fig.1B Electropherogram of qPCR products

（1.DL2000；2. I123/IFN-γ；3.I127/IFN-γ；4.I130/IFN-γ；5.I131/IFN-γ；6.I135/IFN-γ；7.I124/IFN-γ；8.I125/IFN-γ；9.I137/IFN-γ；10.I138/IFN-γ；11.I128/IFN-γ；12.I129/IFN-γ；13.I134/IFN-γ；14.I136/IFN-γ；15.I132/IFN-γ；16.I133/IFN-γ）

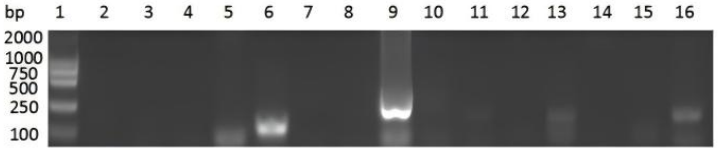


Fig.1C Electropherogram of qPCR products

（1.DL2000；2. I123/IL-1β；3.I127/IL-1β；4.I130/IL-1β；5.I131/IL-1β；6.I135/IL-1β；7.I124/IL-1β；8.I125/IL-1β；9.I137/IL-1β；10.I138/IL-1β；11.I128/IL-1β；12.I129/IL-1β；13.I134/IL-1β；14.I136/IL-1β；15.I132/IL-1β；16.I133/IL-1β）

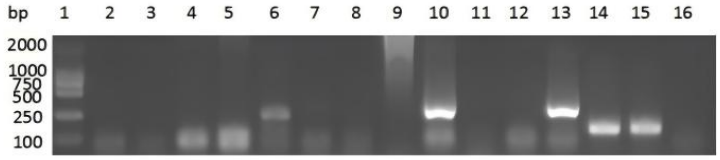


Fig.1D Electropherogram of qPCR products

（1.DL2000；2. I123/IL-6；3.I127/IL-6；4.I130/IL-6；5.I131/IL-6；6.I135/IL-6；7.I124/IL-6；8.I125/IL-6；9.I137/IL-6；10.I138/IL-6；11.I128/IL-6；12.I129/IL-6；13.I134/IL-6；14.I136/IL-6；15.I132/IL-6；16.I133/IL-6）

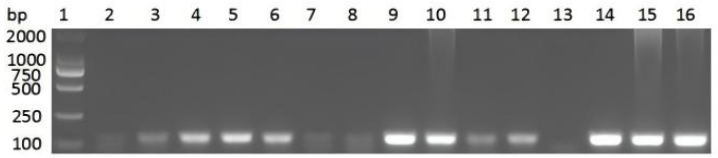


Fig.1E Electropherogram of qPCR products

（1.DL2000；2. I123/TNF-a；3.I127/TNF-a；4.I130/TNF-a；5.I131/TNF-a；6.I135/TNF-a；7.I124/TNF-a；8.I125/TNF-a；9.I137/TNF-a；10.I138/TNF-a；11.I128/TNF-a；12.I129/TNF-a；13.I134/TNF-a；14.I136/TNF-a；15.I132/TNF-a；16.I133/TNF-a）

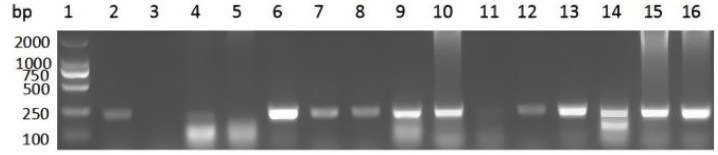


Fig.1F Electropherogram of qPCR products

（1.DL2000；2. I123/IL-10；3.I127/IL-10；4.I130/IL-10；5.I131/IL-10；6.I135/IL-10；7.I124/IL-10；8.I125/IL-10；9.I137/IL-10；10.I138/IL-10；11.I128/IL-10；12.I129/IL-10；13.I134/h-actinβ；14.I136/IL-10；15.I132/IL-10；16.I133/IL-10）

Figure 1. Electrophoresis results of the 15 patients.

3.4 Comparison of Therapeutic Efficacy and Survival Analysis between the Two Groups

As of the final follow-up on December 31, 2025, the median follow-up time in the transplantation group was 59 (51–63) months. During the follow-up period, 10 patients experienced disease recurrence, yielding a recurrence rate of 28.6%. Among them, 5 patients died due to disease progression, with a mortality rate of 14.3%. The remaining 25 patients in the transplantation group remained alive with progression-free survival (PFS) at the final follow-up endpoint. In the control group, the median follow-up time was 62 (45–68) months. By the end of the follow-up, 20 patients experienced disease recurrence or progression during the observation period, representing a recurrence/progression rate of 57.1%. All relapsed patients received later-line treatment regimens for continued therapy. Among them, 9 patients died of multiple organ failure (MOF) secondary to tumor recurrence and progression, with a mortality rate of 25.7%. The remaining 15 patients in the control group remained progression-free at the final follow-up endpoint.

The median DFS time in the transplantation group was 52 (48–60) months, and the median OS time was 59 (51–63) months; the 5-year DFS and OS rates in this group were 66.7% and 70.6%, respectively. In the control group, the median DFS time was 32 (11–64) months, and the median OS time was 62 (45–68) months, with a 5-year DFS rate of 44.7% and a 5-year OS rate of 62.5%. The 5-year DFS rate in the transplantation group was significantly higher than that in the control group (66.7% vs. 44.7%, P = 0.012; Figure 2). However, no statistically significant difference was observed in the 5-year OS rate between the transplantation and control groups (70.6% vs. 62.5%, P = 0.42; Figure 3).

3.5 Survival Analysis of Different Conditioning Regimens

Among the 35 patients in the transplantation group, two different conditioning regimens were administered prior to stem cell infusion: 11 patients received the BEAM regimen (BEAM group) and 24 patients received the BUCY regimen (BUCY group). Survival analysis was performed to compare these two transplant subgroups. The results demonstrated that there were no statistically significant differences in either the 5-year DFS rate or the 5-year OS rate between the two transplant subgroups (81.8% vs 61.8%, P=0.4; 90.9% vs 87.3%, P=0.53, respectively; Figures 4A and 4B).

3.6 Univariate and Multivariate Cox Regression Analysis

The univariate analysis of all 70 patients included the following parameters: group, sex, age, COO, Ann Arbor stage, IPI score, Ki-67 index, extranodal involvement, double-expression status, BMI, tumor size, and B symptoms (Table 2). The univariate analysis results indicated that group, double expression, and BMI were predictive factors for DFS (HR = 2.577, 95% CI = 1.198–5.543, P = 0.015; HR = 3.156, 95% CI = 1.530–6.511, P = 0.002; HR = 4.330, 95% CI = 2.030–9.236, P < 0.001, respectively). Multivariate Cox regression analysis revealed that non-sequential AHSCT consolidation therapy, double expression, and BMI were independent adverse prognostic factors for DFS (HR = 5.583, 95% CI = 2.199–14.175, P < 0.001; HR = 3.240, 95% CI = 1.492–7.037, P = 0.003; HR = 6.225, 95% CI = 2.535–15.282, P < 0.001, respectively).

3.7 Adverse Reactions in the Transplantation Group

No transplant-related mortality (TRM) occurred among the 35 patients in the transplantation group, and all patients developed hematological adverse reactions post-transplantation. Specifically, febrile neutropenia (FN) occurred in 25 cases (71.4%), and bacterial infections were documented in 17 cases (48.6%). The bacterial infections primarily manifested as respiratory tract infections in 7 cases (20.0%), urinary tract infections (UTIs) in 5 cases

(14.3%), and perianal infections in 5 cases (14.3%). Fungal infections were observed in 6 cases (17.1%), which predominantly included oral fungal infections in 4 cases (11.4%) and invasive pulmonary fungal infections (IPFIs) in 2 cases (5.7%). Viral infections occurred in 2 cases (5.7%; Figure 5). The aforementioned infectious adverse reactions were successfully controlled following appropriate symptomatic treatment.

Other non-hematological adverse reactions included hypokalemia in 13 cases (37.1%), vomiting in 11 cases (31.4%), diarrhea in 8 cases (22.9%), elevated alanine aminotransferase (ALT) in 15 cases (42.9%), elevated aspartate aminotransferase (AST) in 15 cases (42.9%), peripheral neuritis in 5 cases (14.3%), cardiac insufficiency in 6 cases (17.1%), rash in 5 cases (14.3%), and fatigue in 12 cases (34.3%). All these symptoms resolved completely after supportive and symptomatic interventions (Table 3)

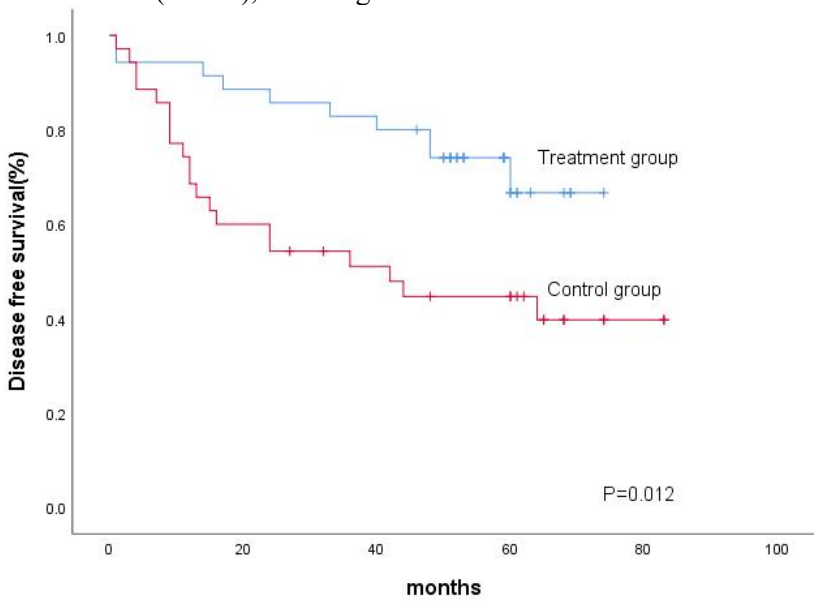


Figure 2. Disease-free survival curves of patients in the treatment group and control group.

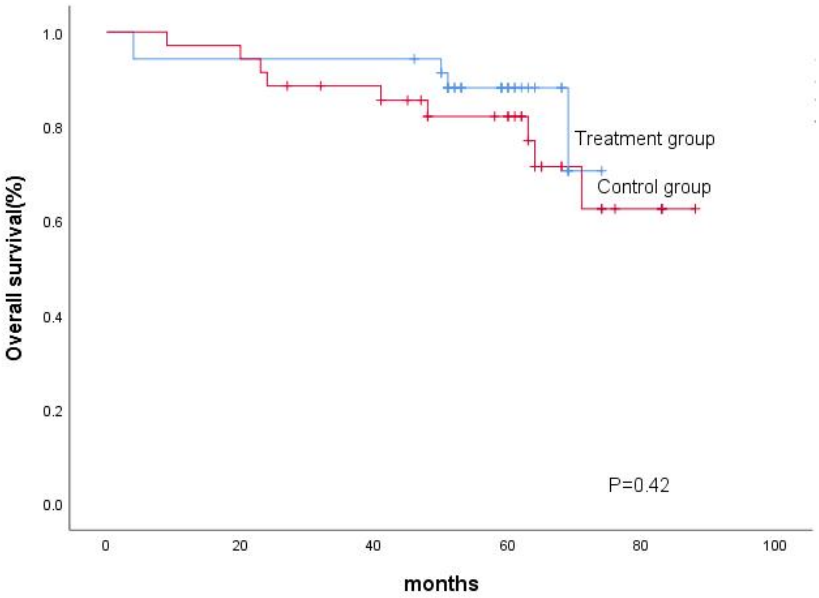


Figure 3. Overall survival curves of patients in the treatment group and control group.

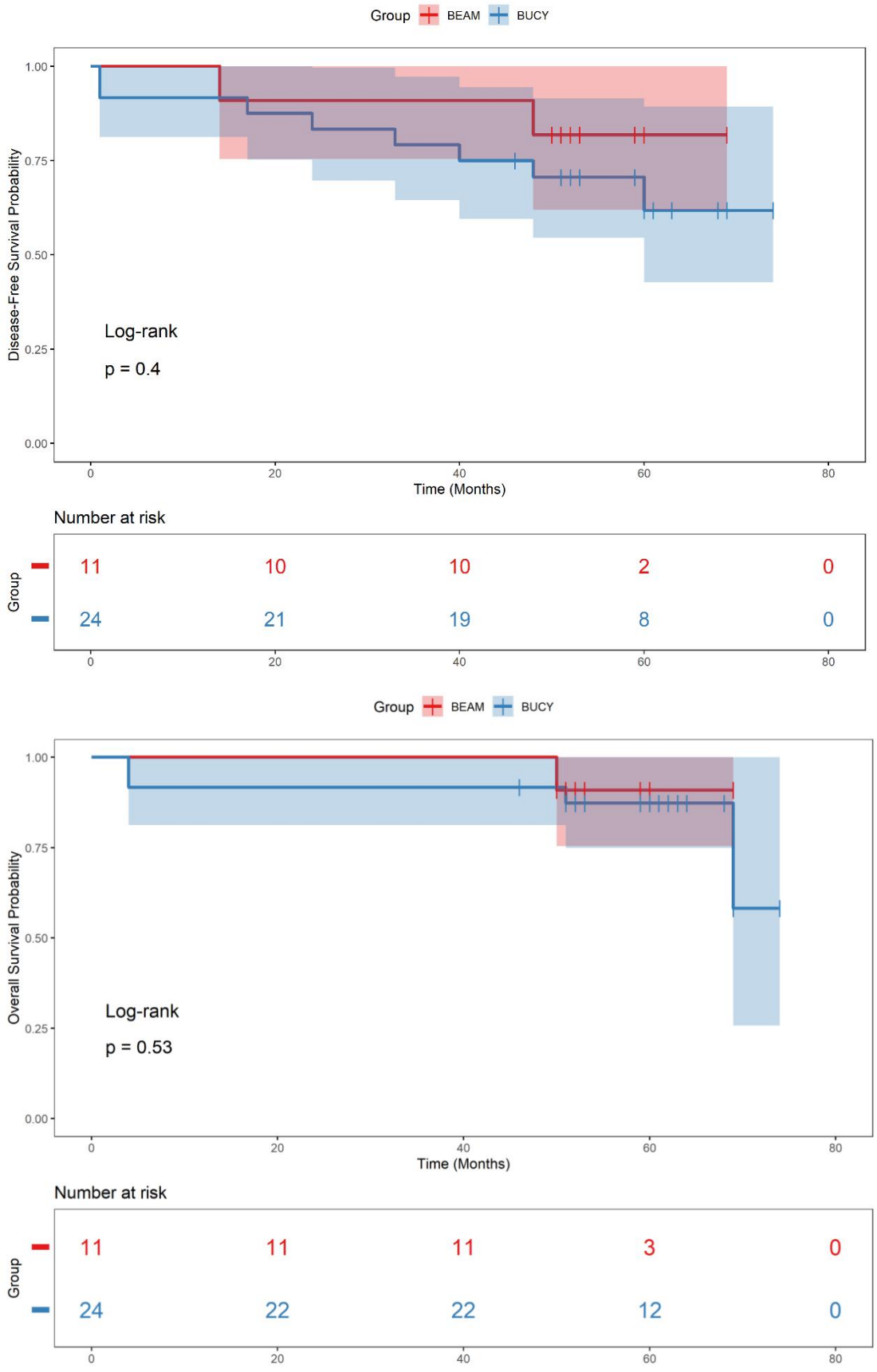


Figure 4. Disease-free (upper, A) and overall (lower, B) survival curves of patients in the BEAM group and BUCY group.

Table 2. Cox regression analysis for disease-free survival (all patients).

	Univariate analysis		Multivariate analysis	
	HR(95%CI)	*P*	HR(95%CI)	*P*
Group(Treatment group, Control group)	2.577(1.198-5.543)	0.015	5.583（2.199-14.175）	＜0.001
Gender(Male, Female)	1.172(0.557-2.467)	0.675		
Age(<60, ≥60 years old)	1.961(0.951-4.043)	0.068		
Cell origin (Non-GCB, GCB)	0.797(0.277-2.292)	0.674		
Ann Arbor stage (I-Arbor stage(I-II,III-IV)	0.946(0.330-2.713)	0.917		
IPI score (3, ⩾4)	1.186(0.542-2.594)	0.670		
Ki-67(<70%,≥70%)	1.314(0.503-3.435)	0.577		
Invasive site (lymph gland, extranodal invasion)	0.807(0.394-1.651)	0.557		
Double expression (No, Yes)	3.156(1.530-6.511)	0.002	3.240(1.492-7.037)	0.003
Bone marrow invasion (No, Yes)	4.330（2.030-9.236）	＜0.001	6.225（2.535-15.282）	＜0.001
Large lump (⩾7.5 cm) (No, Yes）	1.386(0.561-3.419)	0.479		
B Symptom (No, Yes)	0.968(0.415-2.259)	0.940		

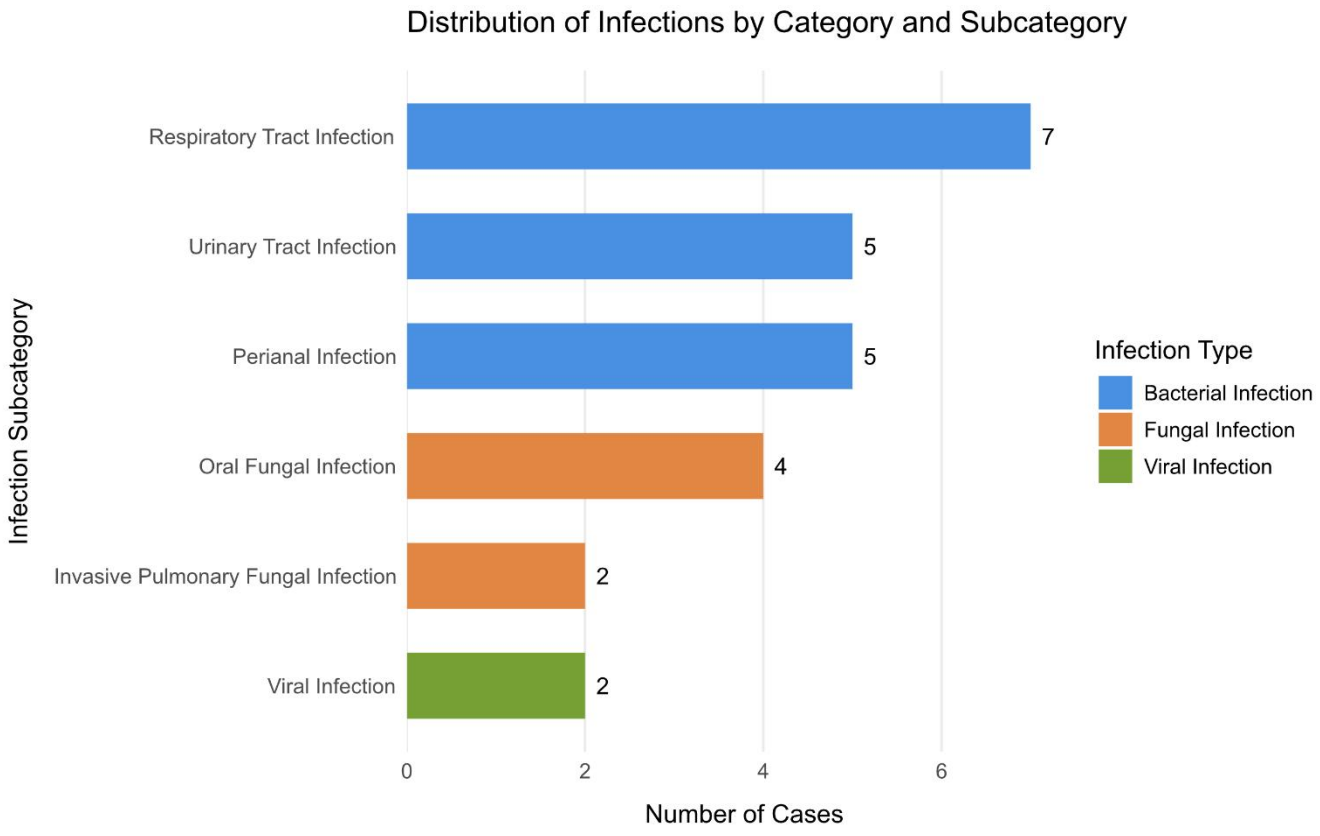


Figure 5. Infection status.

Table 3. Adverse events of patients in the treatment group (n=35).

Adverse events	Any grade (%)
Fever	25(71.4)
Minor infectious agents	17(48.6)
Mycotic infection	6(17.1)
Virus infection	2(5.7)
Hypokalemia	13(37.1)
Vomiting	11(31.4)
Diarrhoea	8(22.9)
Alanine aminotransferase increase	15(42.9)
Aspartate aminotransferase increase	15(42.9)
Peripheral neurotoxicity	5(14.3)
Heart failure	6(17.1)
Rash	5(14.3)
Fatigue	12(34.3)

4. Discussion

DLBCL is a hematological malignancy characterized by pronounced heterogeneity. The clinical manifestations of patients with DLBCL are diverse, with distinct morphological and pathological subtypes, leading to significant variations in disease prognosis. Based on gene expression profiles, DLBCL can be classified into two molecular subtypes: germinal center B-cell-like (GCB) and activated B-cell (ABC), with approximately 12% of DLBCL patients remaining unclassifiable (20). According to immunohistochemical results, DLBCL can be divided into three immunophenotypic subtypes: GCB, non-GCB, and CD5-positive (21). With the emergence and maturation of next-generation sequencing (NGS) technology, a new era of genetic subtyping for DLBCL has begun (22). However, although NGS technology is widely used in clinical practice and has identified over 100 relevant tumor driver genes in DLBCL, the expression of identical gene mutations across different molecular subtypes makes it challenging to apply these findings prospectively for DLBCL subtype classification. Furthermore, there is currently a lack of in-depth research on these genetic mutations, and the understanding of gene-related information remains limited. Consequently, these mutated genes cannot yet be utilized to guide clinical treatment or predict the prognosis of patients with DLBCL (14). Given the high heterogeneity and propensity for relapse and progression in DLBCL, non-cytotoxic regimens can be considered as consolidation therapy for patients achieving CR after chemotherapy to further reduce tumor recurrence and progression. However, results from real-world studies have been underwhelming. An expert panel from the American Society for Transplantation and Cellular Therapy (ASTCT) does not recommend rituximab maintenance therapy for DLBCL (23). Multiple studies have also confirmed that maintenance or consolidation therapy with lenalidomide or targeted agents does not significantly improve patient prognosis (24). Therefore, There is an urgent need to identify effective frontline consolidation strategies for DLBCL patients who achieve CR after chemotherapy, aiming to prolong patient survival and improve outcomes.

AHSCT is a therapeutic modality in which autologous hematopoietic stem cells are collected during disease remission and reinfused into the patient following a conditioning regimen. This process reconstructs the patient's immune and hematopoietic functions, further eradicating residual tumor cells and enhancing therapeutic efficacy (25). Characterized by rapid immune and hematopoietic recovery, few transplant-related complications, high safety, efficacy, and cost-effectiveness, AHSCT has been widely adopted for DLBCL treatment in recent years. In particular, first-line consolidation with AHSCT has emerged as a research hotspot, with several studies yielding encouraging outcomes (26). A study analyzing DLBCL patients who received sequential AHSCT or chimeric antigen receptor T-cell (CAR-T) therapy after chemotherapy showed that patients in the AHSCT group had a significantly superior 2-year PFS rate compared to those in the CAR-T group (66.2% vs. 47.8%, P < 0.001) (15). The 2-year relapse rate also differed statistically (27.8% vs. 48%, P<0.001), indicating that AHSCT can reduce recurrence rates and improve PFS rates compared with CAR-T therapy. Wen et al. investigated intermediate-to-high-risk DLBCL patients divided into a chemotherapy-alone group and a transplantation group (27). They found that the 3-year PFS rates were 59.59% and 81.9%, respectively, and the 3-year OS rates were 64.9% and 87.6%, respectively, suggesting that AHSCT significantly improves the prognosis of intermediate-to-high-risk DLBCL patients. Guo et al. retrospectively analyzed 120 intermediate-to-high-risk DLBCL patients who achieved CR after R-CHOP chemotherapy; 60 patients received sequential AHSCT as frontline consolidation (transplantation group), while 60 patients were followed up observationally (control group) (14). Their results indicated that the 3-year DFS rate in the transplantation group was significantly higher than that in the control group (89.7% vs. 63.9%, P=0.001), suggesting that sequential first-line consolidation with AHSCT after chemotherapy can enhance the DFS rate in newly diagnosed, intermediate-to-high-risk DLBCL patients. To further explore whether AHSCT is a viable consolidation strategy for intermediate-to-high-risk DLBCL patients, this study retrospectively analyzed newly diagnosed, intermediate-to-high-risk DLBCL patients who achieved CR after R-CHOP chemotherapy. Patients were divided into a transplantation group (n = 35) and a control group (n = 35) based on whether they received sequential first-line AHSCT consolidation. The 5-year DFS rate in the transplantation group was significantly higher than that in the control group (66.7% vs. 44.7%, P=0.012), whereas no statistically significant difference was observed in the 5-year OS rate between the two groups (70.6% vs. 62.5%, P=0.42). Multivariate Cox analysis indicated that non-sequential AHSCT consolidation therapy was an independent adverse prognostic factor for DFS (HR = 5.583, 95% CI = 2.199–14.175, P<0.001), confirming that sequential first-line AHSCT consolidation after chemotherapy significantly improves DFS but does not yield an OS benefit. Possible explanations for this include: patients in the control group received timely and effective salvage regimens upon disease recurrence, which prolonged their OS to some extent; some patients in the transplantation group experienced competing risks of death, leading to a decline in the overall OS rate of the transplantation group; or the patient follow-up period was insufficient.

With expanding research into DLBCL, the role of the c-MYC protein in tumors is increasingly recognized by clinical researchers, leading to a gradual rise in the diagnostic rate of double-expression or double-hit lymphoma. Lymphomas overexpressing the c-MYC protein along with the BCL-2 and/or BCL-6 proteins are classified as double-expression lymphoma (DEL), accounting for approximately 30% of all DLBCL patients. Due to its high malignancy and aggressiveness, patients with this subtype exhibit a shorter survival period. In this study, Cox proportional hazards regression analysis was employed to evaluate adverse

prognostic factors affecting DFS in both groups. Double expression was identified as an independent predictive factor for DFS in transplanted patients, with double-expression patients facing a 3.24-fold higher risk of disease recurrence than non-double-expression patients (HR = 3.240, 95% CI = 1.492–7.037, P=0.003), indicating a high risk of recurrence and a poor prognosis for transplanted patients with double expression. A multicenter study analyzing 82 patients with double-expression or double-hit DLBCL (DHL) who achieved CR/PR after first-line treatment—36 of whom received AHSCT consolidation—demonstrated that the 3-year PFS and OS rates in the AHSCT group were superior to those in the non-ASCT group (84.8% vs. 39.9%, P=0.0010; 90.9% vs. 50.6%, P=0.0055, respectively). This indicates that frontline consolidation with AHSCT is an effective therapeutic approach for highly aggressive DLBCL with double expression or double hit, significantly improving patient outcomes (28). These findings align with the results of our study, further underscoring that double-expression patients exhibit high tumor malignancy and aggressiveness, are highly prone to disease recurrence, and carry a poor clinical prognosis. For this patient population, conventional standard chemotherapy regimens fail to achieve durable remission. Attempting sequential first-line AHSCT consolidation after standard chemotherapy may yield superior clinical outcomes.

Conditioning therapy is a critical component prior to AHSCT, playing an essential role in further eradicating residual tumor cells in DLBCL patients and providing marrow space for the engraftment of normal hematopoietic stem cells. The choice of different conditioning regimens may lead to varying clinical efficacies. In this study, among the 35 transplanted patients, 11 received the BEAM regimen and 24 received the BUCY regimen. No statistically significant differences were found in the 5-year DFS and OS rates between the two transplant subgroups (both P > 0.05), suggesting that the two conditioning regimens are not prognostic factors influencing DFS or OS in the transplantation group. Two clinical studies analyzing conditioning regimens for lymphoma patients undergoing AHSCT both indicated that different conditioning protocols had no impact on patient PFS rates (29). These findings are consistent with our results, demonstratingrating that the two conditioning regimens offer comparable efficacy and are not prognostic factors affecting the clinical outcomes of transplanted patients.

AHSCT provides definitive efficacy and relatively favorable safety in the treatment of DLBCL. Multiple studies have indicated that the primary early adverse events of AHSCT include grade Ⅲ -IV myelosuppression, gastrointestinal reactions, and hepatic function impairment, all of which improve after symptomatic treatment (30). In our study, no transplant-related mortality was observed among all transplanted patients. The main adverse reaction was febrile neutropenia, including 17 cases of bacterial infection, 6 cases of fungal infection, and 2 cases of viral infection. Some patients also experienced gastrointestinal reactions and other minor toxicities. All these adverse reactions resolved completely following symptomatic treatment, without affecting the process of hematopoietic reconstitution or causing chronic organ damage. These safety data are consistent with the aforementioned studies, further demonstrating that while various complications may occur with AHSCT in DLBCL patients, the vast majority can be resolved with symptomatic management. This indicates that sequential first-line AHSCT consolidation after R-CHOP chemotherapy is a safe and manageable therapeutic strategy. Furthermore, 15 transplanted patients routinely received the oropharyngeal probiotic BP-OM1 after the initiation of conditioning, and their salivary cytokine levels were monitored. The results suggested that BP-OM1 intervention may alleviate respiratory tract inflammation levels in DLBCL patients undergoing transplantation. Prior studies have also shown that oropharyngeal probiotics can

reduce the risk of respiratory tract infections in patients, which is consistent with our findings (31,32). In future clinical applications, introducing oropharyngeal probiotic therapy could be considered to minimize infectious complications during the transplantation process.

5. Limitation

There are several limitations to this study that should be acknowledged. First, a significant difference in extranodal involvement was observed between the two groups, which may be attributed to the relatively small sample size and potential selection bias. Although extranodal involvement was not identified as a significant prognostic predictor in the Cox regression analysis, the impact of selection bias cannot be entirely ruled out; thus, larger-scale studies are required for further validation. Second, data regarding secondary primary malignancies (SPMs) post-transplantation were not systematically collected, primarily because they were not defined as an observational endpoint during the study design phase, coupled with an insufficiently long follow-up duration. Future studies should extend the follow-up period and systematically evaluate SPMs as a critical safety indicator. Third, pre-transplantation status may serve as an important prognostic factor influencing post-transplant efficacy; however, this study only included DLBCL patients who achieved CR after chemotherapy and failed to incorporate patients who achieved a PR. Finally, with a sample size of only 70 cases, this is a single-center retrospective study. Although a statistically significant difference was observed in DFS between the two groups, no significant difference was found in the OS rate. Consequently, future multicenter clinical trials with larger sample sizes, extended follow-up periods, refined stratification, and the inclusion of more potential high-risk factors are warranted.

6. Conclusions

Among various potential influencing factors, non-sequential AHSCT consolidation therapy, double expression, and BMI were identified as independent adverse prognostic factors for DFS. Throughout the treatment course, comprehensive supportive care measures administered after stem cell infusion ensured that no TRM events occurred in the transplantation group, and all transplant-related adverse events resolved completely after symptomatic management. In conclusion, for patients with newly diagnosed intermediate-to-high-risk DLBCL, sequential first-line consolidation with AHSCT after R-CHOP chemotherapy can significantly improve the DFS rate and enhance clinical outcomes, demonstrating that this therapeutic approach is both safe and manageable.

Declarations

1. ***Consent to publication***
   We declare that all authors agreed to publish the manuscript in this journal based on the signed Copyright Transfer Agreement and followed publication ethics.
2. ***Ethical approval and consent of participants***
   This study was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki and approved by the Medical Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences, Shenzhen Hospital (Ethics Approval No. 2018-23-1).
3. ***Disclosure of conflict of interests***
   We declare that no conflict of interest exists in this work.
4. ***Funding***
   No funding was received for this study.
5. ***Availability of data and materials***
   The minimal dataset necessary to interpret, replicate, and build upon the findings reported in this article is not publicly archived in an open repository due to institutional data governance

regulations and strict patient privacy protections. However, the de-identified datasets analyzed during the current study are available from the corresponding author upon reasonable academic request.

6. Authors' Contributions

XXM and LS: Conceptualization, clinical data collection, statistical analysis, data visualization (plotting), and drafting of the original manuscript. XJ and WYQ: Study design, methodology protocol validation, project administration, and critical revision of the manuscript. GZ and LXY: Clinical supervision, resource provisioning, structural validation, and final approval of the version to be published. All authors have read and approved the final version of this manuscript.

7. **Acknowledgement**

None.

8. Authors' biography

None.

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