Allogeneic Hematopoietic Stem Cell Transplantation: A Salvage Treatment for Relapsed or Refractory Lymphoma

Jing-Shi Wang · Zhao Wang · Yi-Ni Wang ·
Lin Wu · Li Fu · Na Wei

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Abstract To analyze the efficacy and safety of allogeneic hematopoietic stem cell transplantation (Allo-HSCT) in patients with relapsed or refractory lymphoma, the therapeutic efficacy, safety, and survival of 23 patients were evaluated. There were 18 (78.3 %) patients with relapsed lymphoma and 5 (21.7 %) patients with refractory lymphoma. Patients were grafted from human leukocyte antigen (HLA)-matched (10) or mismatched (7) related donors, or matched unrelated donors (6). The responses after Allo-HSCT included 13 (56.5 %) cases of complete remission, 5 (21.7 %) cases of partial remission, and 5 (21.7 %) cases of progressive disease. Overall, 16 of 23 patients were alive at a median follow up of 1,035 days (range 60–2,613), five patients died because of non-relapsed mortality, and two patients died of progressive disease. Progression-free survival rates were 64.6 and 48.4 % at 12 and 24 months, respectively, and overall survival rates were 68.6 and 59.5 % at 12 and 24 months, respectively. Allo-HSCT may be a salvage treatment for relapsed or refractory lymphoma. Myeloablative conditioning regimens may be effective and safe.

Keywords Allogeneic hematopoietic stem cell transplantation · Relapse · Refractory · Lymphoma

Introduction

Treatment of relapsed/refractory lymphoma has always been difficult. The complete remission (CR) rates of salvage chemotherapy for relapsed/refractory lymphoma patients range from 31 to 43 % [1, 2]. Although the importance of high-dose chemotherapy/autologous stem cell transplantation (ASCT) for the salvage treatment of lymphoma has been established, the expected long-term disease-free survival rates are only 0–20 % for patients with refractory, rapidly progressed lymphoma, or patients unresponsive to multiple cycles of high-dose therapy [3]. Thus, allogeneic hematopoietic stem cell transplantation (Allo-HSCT) might be the only therapeutic choice for these patients. Allo-HSCT has two distinct advantages over ASCT: first, the contamination of re-infused hematopoietic stem cells by lymphoma cells can be avoided; and second, residual lymphoma cells in the host can be removed by the graft-versus-lymphoma (GVL) effect. As a result, Allo-HSCT has a high response rate and low recurrence rate compared with ASCT.

Allo-HSCT as a salvage therapy for relapsed/refractory lymphoma has not been widely reported [4, 5]. Freytes et al. [4] analyzed 114 patients with lymphoma who experienced disease relapse after autologous (auto)-HSCT and were subsequently treated with myeloablative allo-HSCT. They showed that the 3-year overall survival (OS) and progression-free survival (PFS) rates were 33 and 25 %, respectively, whereas the 5-year OS and PFS rates were 24 and 5 %, respectively. Bertz et al. [5] analyzed 25 patients with relapsed or refractory non-Hodgkin's lymphoma (NHL; n = 20) or Hodgkin's disease (HD; n = 5) who received an allo-HSCT. Eleven of 25 patients were alive with a median follow up of 618 days (range 383–2,815), with an OS of 44 % at 1 year for all patients.

J.-S. Wang · Z. Wang (✉) · Y.-N. Wang · L. Wu · L. Fu · N. Wei

Department of Hematology, Beijing Friendship Hospital, Capital Medical University, No. 95 Yong'an Road, Xicheng District, Beijing 100050, People's Republic of China
e-mail: wangjingshi987@icloud.com

Furthermore, 8 out of 12 patients were alive after reduced-intensity conditioning, compared with 3 out of 13 after conventional myeloablative conditioning. Herein, we retrospectively reviewed and evaluated the medical records of 23 relapsed/refractory lymphoma patients who underwent Allo-HSCT at the Department of Hematology (Beijing Friendship Hospital) from June 2006 to June 2013.

Subjects and Methods

Research Subjects

Twenty-three relapsed/refractory lymphoma patients undergoing Allo-HSCT at the Department of Hematology, Beijing Friendship Hospital from June 2006 to June 2013 were enrolled in this research. Recurrence refers to relapse that occurs at least 1 month after the CR of lymphoma achieved by first-line treatment. Refractory conditions include CR that cannot be achieved at any time during treatment, disease progresses when partial response has been achieved during treatment, or early recurrence occurs within 1 month after CR. All of the lymphoma cases were diagnosed based on histopathological examination and scored according to the international lymphoma prognostic index (IPI), and the clinical stages were divided according to Ann Arbor clinical staging. Pre-transplant evaluations included physical examinations, bone marrow examinations and neck, chest, abdomen and pelvis computed tomography (CT) examinations. All patients signed an informed consent form before transplantation.

Research Methods

Preparative Regimen

Myeloablative conditioning regimen: patients received total body irradiation (TBI)/cyclophosphamide (Cy) conditioning (TBI; 5 Gy/d, day −6 to −5 of transplant; Cy, 1.8 g/m²/day, day −4 to −3 of transplant) or busulfan (Bu)/Cy conditioning (Bu, 0.8 mg/kg, every 6 h, day −7 to −5 of transplant; Cy, 1.8 g/m²/day, day −4 to −3 of transplant).

Human Leukocyte Antigen Matching and Hematopoietic Stem Cell Mobilization and Collection

Sequence specific primer polymerase chain reaction (PCR–SSP) human leukocytes antigen (HLA) typing technology was adopted for high resolution HLA A, B, C, and DRB1 loci analyses. The donor started to accept subcutaneous injection of 5 µg/kg/day recombinant human granulocyte colony stimulating factor from day −3 of the transplant,

and peripheral blood stem cell collection was initiated on day 0. The target number of CD34+ cells was 2–6 × 10⁶/kg, and the collected peripheral blood stem cells were directly infused back to the patient through a central venous catheter.

Prevention of Infection and Graft Versus Host Disease

Patients were isolated in class 100 laminar flow wards when conditioning commenced. Sulfamethoxazole was used to protect against pneumocystis carinii infection; levofloxacin/cefuroxime against bacterial infection; fluconazole/voriconazole against fungal infection; and ganciclovir against cytomegalovirus (CMV) infection. All patients received cyclosporine A (CsA) + methotrexate (MTX) + anti-thymocyte globulin (ATG) to prevent graft versus host disease (GVHD). CsA 3 mg/kg/day was intravenously administered from day −8, twice a day. Short-term administration of MTX (15 mg/m²/day) was performed on day +1 of transplant, followed by 10 mg/m²/day on days +3, +5, and +11. ATG (Thymoglobuline, 3 mg/kg for HLA matched related transplantation; 10 mg/kg for mismatched related transplantation/matched unrelated donor transplantations) was administered.

Transplantation and Chimerism Detection

Successful transplant was achieved if the neutrophil count was greater than 0.5 × 10⁹/L for three consecutive days, and the platelet count was greater than 20 × 10⁹/L in the absence of platelet transfusion for seven consecutive days. Chimera status was detected by idiochromosome (cases in which the donor and recipient were of the opposite sex) or short tandem repeat polymerase chain reaction fingerprinting (cases in which the donor and recipient were of the same sex).

Evaluation of Efficacy and Adverse Reactions

Clinical evaluation was performed according to International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma, which includes CR, unconfirmed complete remission (CRu), partial remission (PR), stable disease (SD), relapse, and progressive disease (PD) [6]. Acute GVHD was diagnosed based on clinical manifestations including rash, diarrhea, and hepatic function abnormality. Acute GVHD and chronic GVHD were diagnosed and graded according to international standards [7]. All non-hematologic adverse reactions were recorded and graded.

Survival Evaluation

OS represents the time interval between transplantation and the follow-up endpoint or death by any cause. PFS was

defined as the time interval between transplantation and the first occurrence of tumor progression, death, or follow-up endpoint in patients with CR after transplantation. The survival time was computed up to last follow-up in lost to follow-up patients.

Statistical Analysis

Statistical analyses were performed with SPSS version 16.0 (SPSS Inc, Chicago, IL, USA). Data are presented as mean $\pm$ standard deviation (SD) or percentage. Survival was estimated using the Kaplan–Meier method.

Results

Clinical Characteristics

The clinical characteristics of the 23 patients with relapsed/refractory lymphoma are shown in Table 1. The patients included 12 males and 11 females with a median age of 32 years (14–56 years). According to the World Health Organization lymphoma classification, there were four cases of diffuse large B cell lymphoma, four cases of natural killer (NK)/T cell lymphoma (three cases with combined hemophagocytic syndrome), three cases of T lymphoblastic lymphoma, one case of Hodgkin's lymphoma, two cases of follicular lymphoma, two cases of Richter syndrome, one case of skin $\gamma\delta$ T cell lymphoma with combined hemophagocytic syndrome, two cases of anaplastic large cell lymphoma (ALK-), one case of mantle cell lymphoma, one case of angioimmunoblastic lymphoma, one case of Burkitt's lymphoma, and one case of T cell lymphoma. Disease stages were III to IV and IPI scores were 2–5. There were 18 cases (78.3 %) of relapsed lymphoma and five cases (21.7 %) of refractory lymphoma. All patients had accepted 2–20 cycles of chemotherapy before transplant, five patients (21.7 %) accepted local radiotherapy, and the central nervous system was involved in two cases (8.7 %).

The donors included ten HLA-matched related cases, seven mismatched related cases, and six matched unrelated cases. Twenty patients received the TBI/Cy conditioning regimen, while three patients received the Bu/Cy conditioning regimen.

Transplant and Chimerism

All 23 patients were evaluable; white blood cells, red blood cells, and platelets were definitively engrafted in 21 patients. Pure red cell aplasia occurred in one recipient with blood type O receiving transplants from a donor with blood type A, and platelet transplantation was poor in one patient who

received a mismatched related transplant. The median time to when neutrophil levels were higher than $0.5 \times 10^9/L$ and the platelet count was higher than $20 \times 10^9/L$ was 13 days (range 10–16 days) and 12 days (range 9–18 days), respectively. The chimerism was evaluable in all 23 patients, and complete donor hematopoietic chimerism was achieved in 22 patients (95.7 %) at day +28. In one unresponsive Richter syndrome patient conditioned by the TBI/Cy regimen, malignant lymphoma cells accounted for 90.5 % of all cells, while donor-derived cells accounted for 0 % of cells in the bone marrow at day +7 after transplantation, and immunosuppressants were suspended. The donor-type chimerism rate at day +14 was 36.94 %, and $5.1 \times 10^7/kg$ donor derived mononuclear lymphocytes were infused into the recipient. Finally, the donor-type chimerism rate was 75.48 %, and lymphoma cells accounted for 10.5 % of cells in the bone marrow at day +60.

Infection and Adverse Reactions to Conditioning

In total, 16 (69.6 %) patients had neutropenia and fever. Seven (30.4 %) chronic GVHD patients receiving glucocorticoid therapy had severe pulmonary infection, and four patients died of infection unresponsive to anti-infective therapy. Fourteen (60.9 %) patients had CMV viremia, and CMV-DNA turned negative in eight patients receiving ganciclovir and in the other six ganciclovir-resistant patients receiving foscarnet sodium. None of them developed symptomatic CMV disease. Six (26.1 %) patients had grade 3 mucositis, and three (13 %) patients had grade 3 vomiting. Five (21.7 %) patients had grade 3 elevated serum transaminase levels that were alleviated by liver-protective therapies. Two patients with chronic hepatitis B virus (HBV) infection were also noted. In one patient receiving long-term antiviral therapy consisting of entecavir and adefovir, the HBV-DNA was reduced to 10^3 IU/mL and liver function was normal before transplant, and HBV-DNA did not increase during the transplant. In the other patient receiving lamivudine antiviral therapy with HBV-DNA levels below the lowest detection limit prior to transplantation, HBV-DNA increased to 1.1×10^3 U/mL at day +10 after transplantation and changed to negative at day +13 after the treatment had been replaced by antiviral therapy consisting of entecavir and adefovir.

Occurrence of GVHD

Twelve (52.2 %) patients developed acute grade II–IV GVHD, ten of whom responded to glucocorticoid therapy, and two of whom (resistant to glucocorticoid) responded to CD25 monoclonal antibody therapy. Eight (34.8 %) patients developed chronic GVHD, including five cases that progressed from acute GVHD, and three outburst

Table 1 Clinical data of 23 patients with relapsed/refractory lymphoma

Patient no.	Sex	Age	Primary disease	Cycles of chemotherapy	Radiotherapy	Disease status prior to transplantation	Conditioning regimen	Transplant method
1	Male	40	NK/T cell lymphoma (skin) combined with hemophagocytic syndrome	6	No	PD	TBI/Cy	HLA10/10 related donor
2	Female	20	Hodgkin's lymphoma stage IV A	6	Yes	PR	Bu/Cy	HLA10/10 related donor
3	Male	21	Anaplastic large cell lymphoma stage IV B	7	Yes	PD	Bu/Cy	HLA5/10 related donor
4	Female	16	Anaplastic large cell lymphoma stage IV B	4	No	PR	TBI/Cy	HLA9/10 unrelated donor
5	Female	16	NK/T cell lymphoma combined with hemophagocytic syndrome	4	No	PR	TBI/Cy	HLA10/10 unrelated donor
6	Male	32	NK/T cell lymphoma stage III B	6	No	PR	TBI/Cy	HLA10/10 related donor
7	Male	28	T lymphoblastic lymphoma stage IV A	4	Yes	PR	TBI/Cy	HLA5/10 related donor
8	Male	19	T lymphoblastic lymphoma stage IV A	4	No	PD	TBI/Cy	HLA9/10 unrelated donor
9	Male	14	T lymphoblastic lymphoma stage IV B	4	Yes	PD	TBI/Cy	HLA5/10 related donor
10	Female	42	Diffuse large B-cell lymphoma stage IV A	20	Yes	PR	Bu/Cy	HLA10/10 unrelated donor
11	Female	45	Skin $\gamma\delta$ T cell lymphoma combined with hemophagocytic syndrome	4	No	PD	TBI/Cy	HLA10/10 related donor
12	Male	28	Diffuse large B-cell lymphoma stage IV B	5	No	SD	TBI/Cy	HLA10/10 related donor
13	Male	42	Richter syndrome	9	No	PD	TBI/Cy	HLA10/10 related donor
14	Female	30	NK/T cell lymphoma combined with hemophagocytic syndrome	2	No	PD	TBI/Cy	HLA5/10 related donor
15	Male	54	Mantle cell lymphoma stage IV B	7	No	PR	TBI/Cy	HLA10/10 related donor
16	Female	55	Angioimmunoblastic lymphoma stage IV B	7	No	PR	TBI/Cy	HLA10/10 related donor
17	Female	52	Burkitt lymphoma stage III B	6	No	PR	TBI/Cy	HLA9/10 unrelated donor
18	Female	48	Diffuse large B-cell lymphoma stage III A	8	No	PD	TBI/Cy	HLA5/10 related donor
19	Male	56	Follicular lymphoma stage IV A	7	No	PR	TBI/Cy	HLA10/10 related donor
20	Male	54	Follicular lymphoma stage IV A	4	No	PD	TBI/Cy	HLA10/10 related donor
21	Female	18	T cell lymphoma stage IV B	7	No	PR	TBI/Cy	HLA5/10 related donor
22	Female	52	Richter syndrome	9	No	PD	TBI/Cy	HLA10/10 unrelated donor
23	Male	32	Diffuse large B-cell lymphoma stage IV B	8	No	PR	TBI/Cy	HLA5/10 related donor

PR Partial remission, SD stable disease, PD progressive disease, TBI total body irradiation, Cy cyclophosphamide, BU busulfan, HLA human leukocytes antigen

GVHD cases which appeared after immunosuppression reduction. One of these patients died from GVHD.

Disease Response and Relapse

The median follow-up period was 1,035 (60–2,613) days. Among the 23 patients, 13 (56.5 %) achieved CR, 5 (21.7 %) achieved PR, and 5 (21.7 %) developed PD. Among the 18 patients with relapsed lymphoma, 7, 3, and 2 of the 12 patients with PR prior to transplantation developed CR, PR, and PD (both died) after transplantation, respectively. One patient with SD prior to transplant achieved CR after transplant, but died of GVHD 6 months later. Among the five patients with PD before transplant, three achieved CR, one achieved PR, and one developed PD. Among the five patients with refractory lymphoma, two achieved CR, one achieved PR, and two developed PD [one case of T lymphoblastic lymphoma and one case of NK/T cell lymphoma (liver, spleen, and bone marrow metastasis) with combined hemophagocytic syndrome]. The T lymphoblastic lymphoma patient had central nervous system relapse at day +42 and eventually died of combined lung infection.

PFS and OS

As of June 30, 2013, 16 (69.6 %) patients survived and 7 (30.4 %) patients died, five of whom died from transplant-related complications and two of whom died from disease progression. Kaplan–Meier assessment showed that the 12- and 24-month PFS rates were 64.6 and 48.4 %, respectively; and 12- and 24-month OS rates were 68.6 and 59.5 %, respectively (Fig. 1).

Discussion

Treatment of relapsed/refractory lymphoma has always been difficult, and the progression-free and long-term survival rates are still low, even though high-dose chemotherapy and/or radiotherapy and ASCT are available as salvage treatments. Allo-HSCT might be the only treatment option for young patients with highly invasive and bone marrow-involved lymphoma or relapsed lymphoma after ASCT. Our results indicate that the 12- and 24-month PFS rates were 64.6 and 48.4 %, respectively, while the 12- and 24-month OS rates were 68.6 and 59.5 %, respectively, which are superior to previous results [4, 5]. There were seven (30.4 %) deaths among the 23 relapsed/refractory lymphoma cases, and five deaths were due to transplant-related infection and GVHD, which were the primary causes of transplant failure. There were 13 cases of CR and five cases of PR after transplantation among the 23 patients, for a total response rate of

78.2 %. CR might be more readily achieved in relapsed patients compared with refractory patients; however, the differences between the two patient groups could not be statistically analyzed further because of the small number of patients enrolled. Furthermore, among the four patients with malignant lymphoma and combined hemophagocytic syndrome, two patients achieved CR and long-term survival, and one patient achieved CR but died from a lung infection, suggesting that the hemophagocytic syndrome might not be an indicator of poor prognosis for lymphoma patients undergoing Allo-HSCT.

TBI is an important part of the standard Allo-HSCT preparative regimen because of the fact that lymphoma cells are sensitive to radiation therapy and that TBI has anti-lymphoma and immunosuppressive effects [8]. However, TBI has toxic side effects, including mucositis and kidney, liver and significant lung toxicity [9]. In this study, the patients had poor chemosensitivity due to previous, repeated bouts of chemotherapy. TBI-dominant conditioning regimen was applied in 20 patients, but not in three patients with radiotherapy history. The results of this study suggest that TBI promoted stable implantation, the main side effect was mucositis (which was tolerable), and there was no serious impairment of liver, kidney, or lung function or conditioning-related lethal toxicity. The transplant-related mortality within 100 days was 0, suggesting that the TBI/Cy conditioning regimen for myeloablative Allo-HSCT might be safe and effective in lymphoma patients with repeated chemotherapy treatments.

Allo-HSCT plays therapeutic roles through the GVL effect. The GVL effect is closely related to GVHD and relapse after transplantation. The GVL effect was first observed in a Burkitt's lymphoma patient with disease relapse after Allo-HSCT, which was alleviated by dose reduction or discontinuation of immunosuppressants [10]. The presence of the GVL effect has been confirmed by analyzing the relationship between GVHD and disease relapse. In one retrospective study, the relapse rates in patients with chronic GVHD were lower than those without chronic GVHD (0 vs 0.35 %; $P = 0.02$) [11]. Furthermore, the GVL effect is also indicated by the fact that the relapse rate of Allo-HSCT is lower than that of ASCT. The mechanism underlying the GVL effect is quite complicated and not completely understood. The GVL effect might be mediated by donor CD4+, CD8+ T cells, and/or NK cells, and can directly induce tumor cell apoptosis by the Fas/Fas-L pathway and perforin degranulation [12]. In addition, the GVL effect is also regulated by a complex network composed of a variety of immune cells and cytokine pathways, which interact with the host microenvironment. Different types of lymphoma are distinctively sensitive to the GVL effect. For example, many clinical trials have proven that relapsed follicular lymphoma might be

Fig. 1 Progression-free survival **a** and overall survival **b** curves of relapsed/refractory lymphoma

completely responsive to the post-transplant GVL effect [13]. However, the efficacy in relapsed mantle cell lymphoma should be further investigated. The present study enrolled 23 patients with relapsed/refractory lymphoma (Stage III–IV, IPI score 2–5). Twelve (52.2 %) patients had acute grade II–IV GVHD, eight (34.8 %) patients had chronic GVHD, thirteen (56.5 %) patients achieved CR, five (21.7 %) patients achieved PR, and sixteen (69.6 %) patients survived, indicating that Allo-HSCT might be an effective therapeutic method for relapsed/refractory lymphoma, and the GVL effect might be the primary cause for the long-term disease-free survival of these patients.

Donor lymphocyte infusion (DLI) might prevent disease relapse by inducing the GVL effect, and it can be applied in patients at high risk of relapse after Allo-HSCT. Bloor

et al. [14] reported that DLI after Allo-HSCT had good efficacy in 28 patients with low-grade lymphoma, among which seven patients had the GVL effect without significant GVHD, suggesting that DLI is a promising therapeutic strategy to reduce the high risk of relapse. Sohn et al. [15] showed that DLI after Allo-HSCT is an effective immunotherapy, which may be used for the long-term control of disease progression. It has been reported [12] that in one mantle cell lymphoma patient, mantle cell lymphoma cells could still be detected in peripheral blood 1 month after Allo-HSCT, its percentage decreased after the first DLI, and long-term molecular biological CR was achieved after the second DLI. The presence of the GVL effect is also powerfully supported by the fact that molecular biological CR is induced by DLI, which reduces tumor burden. In this

study, a high proportion of lymphoma cells could still be detected in one patient with Richter syndrome after myeloablative bone marrow transplant, the ratio of lymphoma cells was gradually decreased in bone marrow through discontinuation of immunosuppressive agents and DLI, and the ratio of donor derived cells was increased as shown by chimerism detection, which is similar to the previous report.

Interleukin (IL)-2 prevents relapse mainly by improving immune function, which is severely impaired after transplantation. Cytokines are important parts of the tumor antagonistic system in the human body, which directly kills tumor cells, activates effector cells with anti-tumor activities, and regulates the anti-tumor effects of other related factors through the cytokine network [16]. In addition, IL-2 promotes the growth, differentiation, and maturation of T cells and NK cells as a type of growth promoting factor. Porrata et al. [17] found that recovery of the quantity and function of B cells and T cell subsets after HSCT might be delayed more than 18 months and 1 year after transplantation, respectively, and the NK cells recovered most rapidly (about 14 days). IL-2 administered after transplantation promotes the growth, differentiation, and maturation of NK cells so as to eliminate minimal residual disease (MRD) and reduce the incidence of relapse [18]. Interferon (IFN)- α activates CD8+ T cells, increases the sensitivity of CD8+ T cells toward host cells, and promotes GVHD and the GVL effect [19]. In addition, IFN- α increases CD8+ T cells and NK cell-mediated cytotoxicity on residual tumor cells to enhance the GVL effect [19]. In the present study, immunosuppressants were reduced and stopped 90 days after matched unrelated donor Allo-HSCT in one patient with Stage IV A T lymphoblastic lymphoma. There were no GVHD manifestations, including rash, diarrhea, or abnormal liver function. The disease relapsed 6 months later and did not respond to chemotherapy. IFN and IL-2 were used as maintenance treatment. 3-year follow-up showed that the patient had a CR, suggesting that the GVL effect might exist, though there was no evidence of GVHD. IFN and IL-2 can be used for the maintenance treatment of lymphoma that relapsed after Allo-HSCT, which might be related to the GVL effect induced by these factors.

Previous studies have suggested that HBV infection has no significant effect on stem cell transplantation and is not an absolute contraindication of transplantation; however, positive HBsAg and HBV-DNA are important factors associated with hepatitis B relapse after transplantation [20]. There were two patients with chronic HBV in this study; one patient had positive HBV-DNA before transplantation and took entecavir and adefovir for a long time, and there was no elevated HBV-DNA or liver function abnormalities during transplantation. In the other patient,

HBV-DNA turned positive during transplantation, and then turned negative again after adjusting the anti-HBV drug regimen. The above cases suggest that HBV infection is not an absolute contraindication of Allo-HSCT transplantation. Transplantation is available for distinct indications, though there are certain risks. For instance, the hepatitis in the HBsAg (+) patient might be aggravated after Allo-HSCT transplantation; however, the patients might safely withstand the immunosuppression period and avoid hepatitis B progression based on timely adjustment of the antiviral therapy.

In summary, this study suggests that Allo-HSCT is an effective salvage treatment for relapsed/refractory lymphoma, the TBI/Cy conditioning regimen might be safe and effective, and DLI is applicable for patients with a high risk of relapse after Allo-HSCT. However, further studies are needed, as only a small number of patients were enrolled in this study.

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