T Cell-Replete Haploidentical Peripheral Blood Hematopoietic Cell Transplantation for Treatment of T-Lymphoblastic Lymphoma

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Background: There is currently little information on haploidentical hematopoietic cell transplantation (haplo-HCT) for T-lymphoblastic lymphoma (T-LBL). Data about peripheral blood stem cells (PBSC) as a reliable graft source for T-LBL treatment are lacking.

Material/Methods: T-LBL patients who underwent T cell-replete haploidentical peripheral blood hematopoietic cell transplantation (haplo-PBHT) from July 2007 to January 2017 were retrospectively evaluated.

Results: A total of 25 patients (age ≥15 years) with median age of 24 (range 15–51) years were enrolled. The median number of CD34+ cells infused was 5.0 (1.6–14.4) 10⁶/kg. Sustained myeloid engraftment with full donor chimerism was achieved in all patients. The cumulative incidence of grades 2 to 4 acute graft-versus-host disease (GVHD) at day 100 was 24%. Two-year extensive chronic GVHD cumulative incidence was 20%. The 3-year overall survival rate for all patients was 70%. The median survival time of the complete remission (CR) group was better than that of the non-CR group (not reached vs. 9 m) (P<0.01). The relapse rate was 17% for patients who obtained CR and were given haplo-HCT as consolidation treatment.

Conclusions: This study indicates that haplo-PBHT is a safe and effective method for the treatment of T-LBL.

MeSH Keywords: Haploidy • Hematopoietic Stem Cell Transplantation • Precursor T-Cell Lymphoblastic Leukemia-Lymphoma

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Background

T-lymphoblastic lymphoma (T-LBL) is a rare and highly invasive lymphoma, accounting for 1.7% of non-Hodgkin’s lymphoma [1]. It has a higher prevalence in males and often involves the bone marrow, central nervous system (CNS), and mediastinal mass. The clinical manifestations of T-LBL are cough, shortness of breath, and superior vena cava syndrome. In the 1980s, the 5-year progression-free survival (PFS) and overall survival (OS) were only 22% and 32%, respectively, in patients receiving lymphoma-like regimens [2]. In recent years, the complete remission (CR) rate has been significantly improved by using intensive chemotherapy regimens, maintenance therapy, and CNS prophylaxis [3,4]. The CR rate in Asians is 73–80% [5,6]. The data from the MD Anderson Cancer Center showed hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) could lead to CR rate of 91%, with 3-year PFS and OS of 62% and 67%, respectively. In this study, 30% of patients relapsed or progressed within 1 year [3]. Relapse is the predominant problem in patients with T-LBL. It is thought that the recurrence of the disease could be reduced through new drugs. However, a recent phase 2 study found that the relapse rate of the disease remained high, at 31%, even with the addition of nelarabine to hyper-CVAD [7]. Thus, allogeneic hematopoietic cell transplantation (allo-HCT) has been suggested to be an effective consolidation treatment to reduce the relapse rate [6]. However, only 30% of patients have a human leucocyte antigen (HLA)-identical sibling donor, which means that most T-LBL patients will require alternative sources of hematopoietic cells [8]. Recently, haplo-HCT has made much progress and has been widely used in various types of hematological malignancies. Many studies showed that patients who underwent transplantation with grafts from HLA-haploidentical family donors, identical sibling donors, or matched unrelated donors have similar transplantation-related mortality (TRM), relapse rate, OS, and DFS [9]. Both BM and PBSC can be used as stem cell sources for haplo-HCT. Ruggeri’s research showed that survival outcomes are comparable when using PBSC or BM in haploidentical transplantation [10]. Although the use of PBSC increases the risk of acute GVHD, PBSC has certain advantages. For example, compared with collecting BM cells, collecting PBSC has fewer complications to the donor, and when blood groups are incompatible, PBSC does not need red blood cell or plasma depletion. In this situation, there is an urgent need to assess the effectiveness and safety of haplo-PBHCT in the clinical treatment of T-LBL. The present study was designed to analyze the efficacy and safety outcomes of haplo-PBHCT for the clinical treatment of T-LBL. Therefore, in our hospital, haplo-PBHCT was reviewed to determine its feasibility in the treatment of T-LBL.

Material and Methods

Patients

We reviewed the medical records in our center from July 2007 to January 2017. The inclusion criteria were as follows: patients whose age was above 14 years at the time of diagnosis, patients whose pathological diagnoses were based on the morphology and immunohistochemistry of tumor samples or bone marrow aspirates or biopsies, and patients who underwent a haploidentical peripheral blood stem cell transplantation. The Institutional Review Board of the Chinese PLA General Hospital approved this study. All of the patients and their donors provided written informed consent.

Methods

The clinical characteristics and laboratory outcomes at the time of diagnosis were analyzed. Clinical staging for T-LBL was performed using the Ann Arbor staging system. PET-CT or CT scans of the chest or abdomen were collected to obtain the imaging data.

Response assessment

Treatment response was assessed after 6 weeks of induction chemotherapy and 4 cycles of chemotherapy and before and after HCT.

Stem cell source and harvesting

Granulocyte-colony stimulating factor (G-CSF, 5 μg/kg/day) was used to mobilize donors’ peripheral blood stem cells (PBSCs), and PBSCs were harvested on day 1 or 2 (after 5 days of G-CSF). The minimum dose of CD34+ cells was 2×10^6/kg. G-CSF-mobilized T cell-replete peripheral blood as a graft source was infused into the recipient. Erythrocyte depletion was not conducted.

Conditioning regimens and graft-versus-host disease (GVHD) prophylaxis

The haplo-HCT patients received a Bu-based conditioning regimen that included busulfan, cyclophosphamide, carbustine, cytarabine, and antihuman thymocyte immunoglobulin (ATG) or a total body irradiation (TBI)-based conditioning regimen that included TBI, cyclophosphamide, and ATG. All haplo-HCT recipients received cyclosporine A, mycophenolate mofetil, and short-term methotrexate for GVHD prophylaxis.

Statistics

OS was calculated from the date of diagnosis to death. PFS was defined as the time from the best response to disease.
progression or death from any cause. The OS and PFS curves were plotted using the Kaplan-Meier method. The log-rank test was used to compare survival curves. The proportion of each group was analyzed by Fisher’s exact test. A p-value \( \leq 0.05 \) was considered as statistically significant, and all values were 2-sided. All statistical analyses were performed using SPSS 19.0 software.

**Results**

**Patient characteristics**

Between July 2007 and January 2017, 25 patients received haploidentical peripheral blood hematopoietic cell transplantation for T-LBL in the Chinese PLA General Hospital and First Affiliated Hospital of PLA General Hospital. Their ages ranged from 15 to 51 years with a median age of 24 years. The majority of patients were male (16/25). All patients had a stage III/IV T-LBL, and 23 patients had a large mediastinal mass. Seven patients had CNS involvement, and 18 patients had BM involvement at the time of diagnosis. Twenty-four patients showed extranodal infiltration. Cytogenetic analysis was performed in 22 patients. The results showed that 4 patients had chromosome abnormalities. The patients’ characteristics are presented in Table 1.

**Engraftment**

The median number of mononuclear cells infused was 9.1 (5.8–12.6) \( \times 10^8 \)/kg, and the median number of CD34+ cells was 5.0 (1.6–14.4) \( \times 10^6 \)/kg. Sustained myeloid engraftment with full donor chimerism was achieved in all patients. The median time of granulocyte and platelet recovery was 11 (range 10–19 days) and 16 days (range 11–56 days).

**GVHD incidence and severity**

Fourteen patients developed acute GVHD (aGVHD) after transplantation: 8 with grade I aGVHD, 4 with grade II aGVHD, and 2 with grade IV aGVHD. The cumulative incidence of grade II–IV aGVHD at 100 days was 24%. The patients who developed grade IV aGVHD died. Six patients had chronic GVHD (cGVHD), 5 of whom had extensive cGVHD. The 2-year cumulative incidence of extensive cGVHD was 20% (Table 2).

**Transplant-related toxicity and infection complications**

All patients exhibited gastrointestinal events, such as nausea, anorexia, and diarrhea. Eight patients had oral mucositis, 4 had mildly elevated creatinine, 17 had pneumonia and soft tissue infection, 4 had herpes infection, and 14 had cytomegalovirus infection. Hemorrhagic cystitis was observed in 8 cases at day 100. One patient developed posttransplant lymphoproliferative disease and improved after receiving rituximab therapy. There was no death caused by lethal organ toxicities due to the conditioning regimen at 100 days. The most common adverse effects are presented in Table 3.

### Table 1. Patients characteristics.

| Characteristics                  | n (%)                  |
|----------------------------------|------------------------|
| Age (years)                      | Median (range)         |
| Sex                              | Male                   |
| ECOG PS                          | \( \geq 2 \)           |
| Extranodal involvements           | \( \geq 2 \)           |
| Ann Arbor stage                  | III/IV                 |
| Mediastinal disease              | Presence               |
| Pericardial/pleural effusion     | Presence               |
| Splenomegaly                     | Presence               |
| CNS invasion                     | Presence               |
| Serum LDH(IU/L)                  | Elevated               |
| B symptoms                       | Presence               |
| Bone marrow involvement          | Presence               |
| International prognostic index   | Low/low-intermediate    |
| Treatment of responders before HCT| CR                    |
|                                 | Non-CR                 |

CNS – central nervous system; LDH – lactate dehydrogenase; CR – complete remission; PR – partial response; PD – progressive disease.

### Table 2. GVHD outcomes of all patients.

|                              | n (%)                  |
|------------------------------|------------------------|
| Incidence of acute GVHD      | 14 (56%)               |
| Incidence of grades I GVHD    | 8 (32%)                |
| Incidence of grades II–IV GVHD| 6 (24%)                |
| Incidence of chronic GVHD     | 6 (24%)                |
| Incidence of extensive chronic GVHD | 5 (20%)              |

GVHD – graft-versus-host disease

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Survival and relapse

By January 2017, median follow-up time was 42 months (range 4–107 months). Seventeen patients survived and 8 died. Two patients died from GVHD and 6 from disease progression, which was the main cause of death. The relapse rate of patients receiving SCT in CR was 17%.

OS and PFS were 70% and 65% for 3 years, respectively (Figure 1A, 1B). The median survival time of the CR group was better than that of the non-CR group (not reached vs. 11 m, p<0.01) (Figure 1C). Although the median survival time of the TBI-based conditioning group was longer than that of the non-TBI-based conditioning group (102 m vs. 48 m, p=0.37), statistical significance was not reached (Figure 1D). Other factors such as gender, age, IPI, B symptoms, LDH, CNS/BM involvement, and splenomegaly had no effect on OS (Table 4).

Discussion

Here, we present the results of haplo-PBHTC outcomes for T-LBL. A PubMed search revealed no articles specifically investigating T-LBL and haplo-HCT for most T-LBL cases are currently

Table 3. Most common side effects during treatment.

| Side effect                      | No. of patients (%) |
|----------------------------------|---------------------|
| Oral mucositis                   | 8 (32)              |
| Creatinine increase              | 4 (16)              |
| Herpes infection                 | 4 (16)              |
| CMV infection                    | 14 (56)             |
| PTLD                             | 1 (4)               |
| Hemorrhagic cystitis             | 8 (32)              |
| Pneumonia and soft tissue infection | 17 (68)           |

CMV – cytomegalovirus; PTLD – posttransplant lymphoproliferative disease.
captured in clinical studies of acute lymphoblastic leukemia (ALL). In the WHO 2008 classification, LBL and ALL are classified into a single group because of their similar biological characteristics and immunotyping [11]. Moreover, the current recommended treatment of LBL is identical to that for ALL. However, the biological basis of LBL and ALL was found to be dissimilar based on research using animal models, gene expression profiles, second-generation sequencing, and genome-wide sequencing [12,13]. For example, the antigen expression profiles of T-LBL may be closer to those of late-stage intrathymic T cells than those seen in T-ALL [14]. The expression of adhesion molecules and extracellular matrix proteins is higher in LB than in ALL. Clinical studies have found that they were different in the clinical manifestations, risk stratification, treatment, and prognosis [15]. Based on the above findings, further studies on LBL are needed to develop separately from those for adult ALL in order to provide a deeper understanding of and more accurate information on its clinical treatment.

Previous reports on allo-HCT in the last 15 years for the treatment of LBL are listed in Table 5. Our treatment outcomes were similar to those of Seong’s [6] and Xu’s [16] study and better than those of Brammer [17] and Makita’s [18] study. However, patients in these studies had different remission status, which may have affected the clinical results.

Data from the MD Anderson hospital showed that TBI-based conditioning improved 1 and 5-year OS [17]. The prognosis in the TBI group in our study was better than that in the non-TBI group. However, no statistically significant difference was found between the 2 groups, which may be due to the limited number of cases. Our data showed that CR status was associated with longer OS. We also observed that the recurrence rate was very low (17%) in high-risk patients who obtained CR and were given haplo-HCT as consolidation treatment. Our study results suggest that the upfront use of allo-HCT could be an effective consolidation treatment for patients who achieved CR.

Several studies reported that many Asian T-LBL patients cannot tolerate planned chemotherapy treatment due to the severe adverse effects [6,18]. Genetic differences may play a role in this situation [19]. These patients were more likely to relapse and have bad prognosis due to inadequate treatment. Therefore, using allo-HCT as consolidation therapy is a good option in reducing disease relapse.

### Table 4. Risk factors for clinical outcomes.

| Characteristics       | Groups                        | P value |
|-----------------------|-------------------------------|---------|
| Gender                | Female                        | 0.6298  |
|                       | Male                          |         |
| Age (years)           | ≥33                           | 0.9083  |
|                       | <33                           |         |
| IPI                   | Low/low-intermediate          |         |
|                       | High-intermediate/ high       | 0.8220  |
| B symptom             | Presence                      | 0.1391  |
|                       | Absence                       |         |
| Serum LDH             | Elevated                      | 0.1938  |
|                       | Normal                        |         |
| BM or CNS involvement | Presence                      | 0.8542  |
|                       | Absence                       |         |
| Splenomegaly          | Presence                      | 0.1938  |
|                       | Absence                       |         |
| Status before         | CR                            | <0.01   |
| transplantation        | Non-CR                        |         |
| Conditioning regimen  | TBI-based                     |         |
|                       | Non-TBI-based                 | 0.37    |

CNS – central nervous system; LDH – lactate dehydrogenase; IPI – international prognostic index; BM – bone marrow.

### Table 5. Studies on allogeneic stem cell transplantation in T-lymphoblastic lymphoma.

| Authors          | Country    | Year       | Disease status          | Patients number | DFS/PFS   | OS     |
|------------------|------------|------------|-------------------------|----------------|-----------|--------|
| Shinichi [14]    | Japan      | 2000–2013  | CR/PR/ Less than PR     | 4/4/7 (15)     | 24% (2-yr)| 37% (2-yr) |
| Jonathan [15]    | U.S.       | 1990–2015  | –                       | 31             | 48% (1-yr)| 52% (1-yr)| 41% (3-yr)|
| Seong [6]        | South Korea| 2000–2011  | –                       | 8              | 75% (3-yr)| 75% (3-yr) |
| Xu [16]          | China      | 2004–2015  | CR/PR/PRD               | 6/2/1          | 66% (2-yr)| 66% (2-yr) |
| Present study    | China      | 2007–2017  | CR/ Less than CR        | 18/7 (25)      | 65% (3-yr)| 70% (3-yr) |

DFS – disease-free survival; PFS – progression-free survival; OS – overall survival; CR – complete remission; PR – partial remission.
Given the limited family member and genetic differences, approximately two-thirds of patients had no HLA-matched related sibling or donor. It can take several months to find a donor, increasing the risk of recurrence. Moreover, maintenance and consolidation of treatment during the waiting period can produce unnecessary chemotherapy-related toxicity. Sometimes, even if a suitable donor is found, some patients lose the opportunity for transplantation due to disease progression. Therefore, timing of transplantation is very important in HCT. Makita’s research data showed that when LBL patients miss the best transplant time, their prognosis becomes much worse [18]. The rapid and near-universal availability of donors is an advantage of haplo-HCT, which enables the treatment for more LBL patients.

Many studies have shown that haplo-HCT is a safe and effective option for patients without a donor and has comparable results to HLA-matched related donor (MRD) and HLA-matched unrelated donor (MUD) [20,21]. Both BM and PBSC could serve as the graft for haplo-HCT. PB and BM grafts have differing patterns of treatment and both have their own advantages and disadvantages. Compared to BM graft, PB graft has more CD34+ stem cells and T cells and is safer and easier to collect. PB grafts may have more severe aGVHD and stronger GVT effect due to the larger number of T cells and the higher engraftment rates linked to the larger number of CD34+ stem cells. PB grafts increase the risk of aGVHD, but NRM, LFS, and OS were similar compared to BM grafts [10]. This may be due to the substantial improvements in supportive care. We initiated the study of unmanipulated haplo-PBSCT for the treatment of high-risk hematologic malignancies since 2007. By using G-CSF-mobilized PBSCs and immunosuppressive agents, our transplantation center has achieved acceptable GVHD incidence rates and low NRM rates. Thus, we applied haplo-PB-HCT to T-LBL and the results suggest that haplo-HCT is a stable and reliable treatment for T-LBL.

Allo-SCT remains the most effective treatment for many lymphatic malignant diseases such as those with persistent or relapsing MRD, chemotherapy-resistance, or experiencing relapse after initial CR [22]. In this situation, haplo-SCT is a valuable treatment option because donor availability still remains a significant challenge for many patients. Santoro’s research on 208 ALL patients (44% in CR1) receiving haplo-SCT showed that OS and LFS at 3 years were 33% and 31% [23]. Results of a study by Xu et al. on 26 patients with refractory, relapsed, or highly aggressive NHL who received Haplo-HCT showed the estimated 2-year OS and DFS rate was 71.60% and 48.90%, respectively [18]. Therefore, haplo-SCT may be considered a valid option for adult patients with lymphatic malignant diseases who lack HLA-identical donors, preferably in early disease status.

Conclusions

Our results show that haplo-PBSCT can be safely and effectively applied for the treatment of T-LBL. However, further studies with large sample sizes are needed to support our results.

Conflicts of interest

None.

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