RESEARCH ARTICLE

Allogeneic Hemopietic Stem Cell Transplants for the Treatment of B Cell Acute Lymphocytic Leukemia

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Abstract

Objective: Explore the feasibility of allo- hemopietic stem cell transplants in treating patients with B cell acute lymphocytic leukemia. Methods: Between september 2006 and February 2011, fifteen patients with B cell acute lymphocytic leukemia (ALL) were treated by allo-hemopietic stem cell transplants (HSCT). Stem cell sources were peripheral blood. Six patients were conditioned by busulfan (BU) and cyclophosphamide (CY) and nine patients were conditioned with TBI and cyclophosphamide (CY). Graft versus host disease (GVHD) prophylaxis regimen consisted of cyclosporine A (CSA), methotrexate (MTX) and mycophenolatemofetil (MMF). Results: Patients received a median of 7.98×10^8·kg^-1 (5.36-12.30×10^8·kg^-1) mononuclear cells (MNC). The median time of ANC> 0.5×10^9/L was day 12 (10-15), and PLT> 20.0×10^9/L was day 13 (11-16). Extensive acute GVHD occurred in 6 (40.0%) patients, and extensive chronic GVHD was recorded in 6 (40.0%) patients. Nine patients were alive after 2.5-65 months follow-up. Conclusion: Allogeneic stem cell transplant could be effective in treating patients with B cell acute lymphocytic leukemia.

Keywords: Hematopoietic stem cell transplants - acute lymphocytic leukemia

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Introduction

Adult acute lymphoblastic leukemia (ALL), accounts for 15% ~ 20% of adult acute leukemia (Rowe JM et al., 2005). Complete response rate (CR) of first line chemotherapy is more than 80%. But the recurrence rate is very high, and the prognosis is poor. Long-term overall survival rate (OS) is only 30%-40% (Rowe et al., 2010). Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is the only method to cure adult ALL. In this study, fifteen patients with B cell ALL were treated by HSCT, including unrelated Allo-HSCT and sibling- HSCT.

Materials and Methods

Clinical data

Between September 2006 and February 2011, 15 patients (10 male and 5 female) with B cell ALL diagnosed in Department of Hematology of Changzhou First People’s Hospital were treated by HSCT. The median age of patients was 34 (19 ~ 46) years. States of patients in transplantation: 13 patients achieved complete remission on first line chemotherapy (CR1), 2 achieved complete remission on second line chemotherapy (CR2). The median white cell count at diagnosis (WBC) was 12 × 10^9/L (2-235 × 10^9/L). 5 patients were accompanied with lymph node enlargement, 2 with leukemia of central nervous system. Chromosome analysis was available in 12 patients: 8 patients with normal karyotype, 2 were confirmed with Philadelphia chromosome positive. Before transplantation, all patients achieved bone marrow CR, and the median course of chemotherapy was 5 (3-8); the median time from diagnosis to transplantation was 181 (105-274) days. For total 15 donors, 6 donors were HLA completely matched; 9 were unrelated, 5 had 1 locus mismatched; 4 had 2 locus mismatched. Seven were male donors, 8 were female. Six donors had same blood type, 4 had main different blood type, 5 had minor different blood type.

Treatment

Conditioning treatment A: cytarabine (Ara - C) 4 g, m - 2, d - 1 x 2 d, intravenous infusion (iv. -10, -9 days); Busulfan (Bu) 3.2 mg, 1 kg^-1, d-1x 3d, iv. (-8, -7, -6days). Cyclophosphamide (Cy) 1.8 g, m - 2, d - 1 x 2 d, iv. (- 5, -4 days); Semustine (Me - CCNU) 250 mg, m - 2, d - 1 x 1 d, oral (3 days). Six patients were conditioned by this method. Conditioning treatment B: TBI 10 ~ 12 gy, irradiation in three day and a total of six times (- 7, -6, -5 days). Cy 60 mg, kg^-1, d - 1 x 2 d, iv. (- 4, -3 days). Nine patients were conditioned by this method. Except for HLA sibling, anti-Human thymocyte globulin (ATG) 5 mg, 1
kg⁻¹, d - 1 × 2-3 d were used in conditioning treatment. The prevention and treatment of GVHD: Cyclosporin A (csA), mycophenolate mofetil (MMF) and short-course methotrexate (MTX) were used to prevent graft versus host disease (GVHD). CsA 2.5-3 mg, kg⁻¹, d - 1, was started intravenously from d -1 and continued to d + 28, orally maintained, with a maintenance blood concentration within 200-400 ng/ml. MMF 1.0 g/d, orally, reduced after transplantation at day 28. MTX 15 mg • m⁻², iv., + 1 d after transplantation; MTX 10 mg, m - 2, iv., on + 3 d, + 6 d and d + 11 after transplantation. Diagnostic and classification criteria of GVHD were in line with previous report [6]. When acute or chronic GVHD were diagnosed, methylprednisolone was added.

**Supportive care:** granulocyte colony stimulating factor (g-csf) 5μg, kg⁻¹, d -1 was administered on 5 ~ 7d after transplantation, till WBC reached 4.0 × 10⁹ / L. When PLT was less than 20 × 10⁹ / L, the patient will receive platelet infusion. Ten days to two days before transplantation, ganciclovir 250 mg, once daily, was administered to prevent cytomegalovirus (CMV) infection, and CMV-DNA was monitored. Prostaglandin E1 was used to prevent hepatic vein occlusion disease (VOD). Hydration, alkalinizing urine and Mesan were adopted to prevent hemorrhagic cystitis. All blood products infused should be irradiated with 25Gy Co60.

**Detection of engraftment evidence:** WBC count recovered to 1 × 10⁹/L or neutrophil count recovered to 0.5 x 10⁹/L for 3 consecutive days was the evidence of graft survival. Direct evidence: ABO blood type of patient was tested the same with the donor. Sex chromosome detection, polymorphisms of short tandem repeats (STR) were also conducted. Indirect evidence was suggested by hematopoietic reconstruction and GVHD.

## Results

Clinical data on 15 patients with hematopoietic reconstruction and survival status after HSCT (in Table 1).

<table>
<thead>
<tr>
<th>Serial number of patient</th>
<th>Gender</th>
<th>Age</th>
<th>condition before transplantation</th>
<th>The donor and match of HLA</th>
<th>The input cell number (10⁸/kg)</th>
<th>Hematopoietic reconstitution days (day)</th>
<th>Platelet (10⁹/kg)</th>
<th>survival time (month)</th>
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<tr>
<td>1</td>
<td>Male</td>
<td>22</td>
<td>CR1 5/6 unrelated</td>
<td></td>
<td>6.02</td>
<td>12</td>
<td>3.28</td>
<td>14</td>
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<tr>
<td>2</td>
<td>Male</td>
<td>25</td>
<td>CR1 6/6 sibling</td>
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<td>7.25</td>
<td>11</td>
<td>5.02</td>
<td>12</td>
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<tr>
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<td>Female</td>
<td>24</td>
<td>CR1 10/10 unrelated</td>
<td></td>
<td>7.41</td>
<td>13</td>
<td>5.10</td>
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<tr>
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<td>42</td>
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<td>6.35</td>
<td>13</td>
<td>3.90</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>30</td>
<td>CR2 9/10 sibling</td>
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<td>13</td>
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</table>

### Hematopoietic reconstruction

All 15 patients were confirmed to be hematopoietically reconstructed. In table 1, count of peripheral blood nucleated cell transfused, count of CD34 cells, time period of neutrophil count ≥0.5 × 10⁹ / L and platelets ≥ 20 × 10⁹ / L, were summarized. All patients received hematopoietic reconstruction. The median time of ANC>0.5×10⁹/L was day 12 (10-15), and PLT> 20.0×10⁹/L was day 13 (11-16).

### Transplant related complications

A total of 6 (40.0%, 6/15) patients were recorded with I - IV aGVHD, including 2 patients with I °, one patient with II °, 1 patient with III °, 2 patients with IV °. Four of 6 patients were effectively treated with CsA, glucocorticoid combined with MMF. One patient (serial number 1) was discovered skin congestive rash on body and limbs (less than 50% body surface area), with diarrhea (6 ~ 10 times/d), on +32 day, without jaundice, and was diagnosed with acute III ° GVHD. This patient was treated with prednisolone 2 mg, kg⁻¹, d -1, budesonide, Fk506 etc, and the symptoms were relieved on +53 days, after gradually stop immunosuppressants, rash, transaminase elevations, dry eyes, oral mucositis etc., appeared. This patient was then diagnosed with extensive chronic GVHD, then re-treated with Fk506 and oral prednisone, during follow-up, this patient was still alive.

Another patient (serial number 14) was also discovered skin congestive rash on body and limbs (more than 50% body surface area), with diarrhea (10 ~ 15 times/d), without jaundice, and was diagnosed with acute IV ° GVHD. Although treated with prednisolone 2 mg, kg⁻¹, d -1, MTX, budesonide and Fk506 , the condition was not improved, and the patient died of severe intestinal GVHD on +75 day.

The third patient (serial number 15) complained symptoms of diarrhea (15 ~ 20 times/d) from +42 day, and diagnosed with acute GVHD IV °. The patient was treated with prednisolone, MTX and budesonide. Condition of the patient was improved, the stopped immunosuppressant on +320 day and did not have obvious GVHD again. Six patients were diagnosed with cGVHD. Patients with
HSCT had a higher recurrence rate, while the patients allo-HSCT, had the same treatment effect as with sibling (1993-2003) at a high risk of ALL who were treated with. Unrelated donor transplantation was an important source 30% of patients could be matched with an HLA donor. rate (Terwey et al., 2009). However, only less than disease-free survival (DFS), and reduce the mortality survival (OS) in patients with high-risk ALL, prolong transplantation could significantly improve the overall transplant could be effective in treating patients with B cell acute lymphocytic leukemia.

References


Lqbal Z (2014). Molecular genetic studies on 167 pediatric ALL patients from different areas of Pakistan confirm a low frequency of the favorable prognosis fusion oncogene


