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), methotrex ate (MTX) and mycophenolatemofetil (MMF). Results: Patients received a median of $7.98\times108\cdot kg^{-1}$ ($5.36\text{-}12.30\times10^{8}\cdot kg^{-1}$) 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 lymphocyti 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

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Table 1. Clinical Data on 15 Patients with Hematopoietic Reconstruction and Survival Status after HSCT

Serial number of patient	Gender	Age	condition before transplantation	The donor and match of HLA	The input cell number		Hematopoietic reconstitution days (day)		survival time (month)
					karyocyte (10^8/kg)	CD34+ cells (10^6/kg)	Implantation of Granular cell	Platelet engraftment	
1	Male	22	CR1	5/6 unrelated	6.02	3.28	12	14	65
2	Male	25	CR1	6/6 sibling	7.25	5.02	11	12	59
3	Female	24	CR1	10/10 unrelated	7.41	5.10	13	12	20
4	Male	36	CR1	9/10 sibling	5.62	2.98	15	16	44
5	Male	46	CR1	8/10 unrelated	8.90	4.89	12	14	14
6	Male	42	CR1	9/10 sibling	6.35	3.90	13	15	15
7	Female	30	CR2	9/10 sibling	7.10	5.02	12	13	12.5
8	Male	30	CR1	8/10 unrelated	8.02	6.8	13	12	15
9	Female	34	CR1	10/10 sibling	5.36	3.12	14	15	13.5
10	Male	39	CR1	9/10 unrelated	9.25	7.02	10	11	28
11	Male	19	CR1	10/10 sibling	8.68	6.52	10	11	28
12	Female	29	CR1	8/10 sibling	12.30	9.03	11	12	36
13	Male	41	CR2	10/10 unrelated	7.98	6.60	12	15	15
14	Male	45	CR1	8/10 sibling	11.26	6.82	13	12	2.5
15	Female	26	CR1	10/10 sibling	10.23	8.60	12	11	22

kg^{-1}, d - 1 x 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 x 10^9 / L. When PLT is less than 20 x 10^9 / 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, alkalizing 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 × 10^9/L or neutrophil count recovered to 0.5 x 10^9/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).

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 x 10^9 / L and platelets ≥ 20 x 10^9 / L, were summarized. All patients received hematopoietic reconstruction. 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).

Transplant related complications

A total of 6 (40.0%, 6/15) patients were recorded with I - IV ° aGVHD, including 2 patients withI °, 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

serial number 5, 6, 12, complained symptoms, e.g. skin rash, transaminase elevation, jaundice, dry eyes, mucositis etc., and diagnosed with chronic diffuse GVHD on +100 day. They were treated with methyl prednisone 40 mg/d dragon, CSA 150 mg/d or FK506, then symptoms of chronic GVHD were markedly improved. Patients with serial number 3 and 8, complained symptoms of dry eyes, oral mucositis, on + 100 day of transplantation, and were diagnosed with chronic GVHD. Symptoms of chronic GVHD in these two patients were improved without special treatments.

Other complications

Three patients (20%) had hemorrhagic cystitis (HC). they were cured by hydration, alkalizing urine, and Mesan. CMV infection was confirmed in 4 patients, after been treated with Ganciclovir and foscarnet sodium, CMV became negative. Interstitial pneumonia was developed in patient with serial number 5 on +112 day. After this patient was treated with anti-viral therapy and immunoglobulin, his condition was improved.

Patient follow-up and survival status

The deadline of follow-up was on February 1st, 2012, the follow-up time was 2.5-65 months. Patients with serial number 3, 7, 9, 13 relapsed and died on +703 day, +380 day, +405 day, and + 460 day after transplantation respectively. Patient with serial number 8 had t the recurrence in right testis on +220 day, and was treated by resection of the right testis. He was also diagnosed with bone marrow involvement on +270 day, his condition was stable after chemotherapy. The rest nine patients were alive with a median survival time of 840 (420-1970) days, including one patient survived more than 65 months.

Discussion

In China, B-ALL accounts for 70.5% of ALL9 (Li X et al., 2012) Treatment strategy for patients who responded to chemotherapy, is preferentially to conduct sibling allogeneic transplantation, followed by HLA unrelated umbilical cord blood transplantation (UCBT), autologous transplantation, half consistency, and consolidated maintain chemotherapy (Pui et al., 2006; Abdel-Aziz et al., 2013; Dunna et al., 2013; Ozbas-Gerceker et al., 2013; Jiang et al., 2013; Soheila et al., 2013; Tharnprisan et al., 2013; Dunna et al., 2014; Iqbal et al., 2014; Mehde et al., 2014; Niu et al., 2014; Shaikh et al., 2014; Wang et al., 2014). French study suggests that allogeneic stem cell transplantation could significantly improve the overall survival (OS) in patients with high-risk ALL, prolong disease-free survival (DFS), and reduce the mortality rate (Terwey et al., 2009). However, only less than 30% of patients could be matched with an HLA donor. Unrelated donor transplantation was an important source of HSCT. Tsuchida et al. reported1233 Japanese patients (1993-2003) at a high risk of ALL who were treated with allo-HSCT, had the same treatment effect as with sibling HSCT (Masa et al., 2005)

Studies with large sample size suggested that sibling HSCT had a higher recurrence rate, while the patients received matched unrelated donor transplantation (MUD) - HSCT had higher treatment related mortality (TRM), therefore, obvious difference in OS was not found. Factors that could influence this result included treatment intensity before HSCT, conditioning, immunosuppressant after HSCT, and experience of HSCT center, etc. (Yuan et al., 2005)

In UKALL XII/ECOG 2993, results of 1522 adult patients suggested that T-ALL had a better prognosis than B-ALL (5 years OS rate to 48% and 41%, p=0.003), but the difference was mild in multivariate analysis. In France GOELAMS study, no difference was found (Hunau ltM et al., 2004). ALL relapse is the main reason of treatment failure by HSCT, and is related to patient age, disease status before transplantation, conditioning, and the effect of GVL (Chen et al., 2004). For patients with recurrence after transplantation, the most effective treatment is re-transplantation and donor lymphocyte infusion (DLI) (Xiao et al., 2007) . Nine 15 patients (60%) in this study had a median survival time for 840 day, without leukemia recurrence. Among five patients with recurrence after transplantation, 4 died of recurrence. One patient achieved bone marrow complete remission after induction chemotherapy, and was not treated with DLI. Six of 15 patients diagnosed with chronic GVHD. One patient diagnosed with GVHD after transplantation, but still had recurrence, and eventually died of recurrence. Thus, the effect of GVHD in the prevention of ALL recurrence is limited.

In conclusion, allogeneic stem cell transplant could be effective in treating patients with B cell acute lymphocytic leukemia.

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