

Allogeneic hematopoietic stem cell transplantation for patients with acute leukemia

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Objective: The purposes of this study were to assess the efficacy of allogeneic hematopoietic stem cell transplantation (HSCT) for acute leukemia (AL) and analyze the factors affecting the prognosis of these patients.

Methods: The clinical and follow-up data of 93 AL patients (median age, 30 years) undergoing allogeneic HSCT in Xiangya Hospital over the past 12 years were collected, and the potential factors affecting the efficacy and prognosis of allogeneic HSCT patients were determined.

Results: Hematopoietic reconstitution was achieved in 90 patients. At the last follow-up, the incidences of severe acute graft versus host disease (aGvHD) and extensive chronic GvHD (cGvHD) were 14.0% and 20.0%, the 3-year cumulative incidence of transplantation related mortality (TRM) and relapse rate were $16.8\% \pm 6.1\%$ and $21.3\% \pm 6.7\%$, and the estimated 3-year overall survival (OS) and disease-free survival (DFS) of the patients were $64.6\% \pm 5.4\%$ and $56.5\% \pm 5.5\%$, respectively. Univariate analysis indicated that age older than 40 years, HLA mismatch, and severe lung infection within the first 100 days after transplantation were risk factors for severe aGvHD, age older than 40 years, HLA mismatch, severe lung infection within the first 100 days after transplantation, and severe aGvHD were risk factors for TRM, high-risk AL and lack of cGvHD were risk factors for relapse (all $P < 0.05$). Survival estimation showed that HLA mismatch, severe lung infection occurring within the first 100 days post-transplantation, high-risk AL severe aGvHD and lack of cGvHD were risk factors associated with poor prognosis (all $P < 0.05$). Further multivariate analyses revealed that severe lung infection within the first 100 days post-transplantation, severe aGvHD and lack of cGvHD were independent risk factors for unfavorable outcomes (all $P < 0.05$).

Conclusions: Allogeneic HSCT can improve the DFS of AL patients, and severe lung infection within the first 100 days post-transplantation, severe aGvHD and lack of cGvHD are independent risk factors affecting the prognosis.

Key Words: Leukemia; hematopoietic stem cell transplantation (HSCT); graft-versus-leukemia effect



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Introduction

Over the past nearly 30 years, the chemotherapy has been the most common and guideline-recommended first-line treatment modality for acute leukemia (AL) in young patients (1,2). Although standard induction chemotherapy

results in complete remission (CR) in 60% to 80% of the young AL patients, relapse will occur in majority of them within months if no potent post-remission treatment is given to eradicate residual leukemic cells. Especially in patients with relapsed, refractory, or other high-risk AL, long-term disease-free survival (DFS) is rare even after

achieving a remission to high-dose chemotherapy (3-5). Therefore, how to improve the long-term survival rate of AL patients is still a critical issue (6,7).

Allogeneic hematopoietic stem cell transplantation (HSCT) that includes allogeneic bone marrow transplantation (BMT), allogeneic peripheral blood stem cell transplantation (PBSCT) and cord blood transplantation (CBT), has become an important approach for treatment of a range of blood diseases as well as some solid tumors and immunodeficiency disorders (8-10). Nowadays, allogeneic HSCT is considered the only curative therapy for AL, because of its distinct advantage of the graft-versus-leukemia (GvL) effect. However, several problems remain to be further determined, such as the selection of the suitable candidates for HSCT, optimal sources of donors, and timing for the procedure as well as preparative regimen, and how to overcome the transplant rejection or graft versus host disease (GvHD), and control or avoid the transplant-related complications (11-13). Here, we reviewed 93 AL patients less than 60 years old (median age, 30 years) who underwent allogeneic HSCT during the past 12 years in Xiangya hospital, for assessing the efficacy of allogeneic HSCT in these patients and analyzing the influential factors of prognosis.

Patients and methods

Patients

Between July 2000 and March 2012, a total of 93 AL patients underwent allogeneic HSCT in our hospital, of whom 57 cases were males and 36 were females with a median age of 30 years (range, 8-46 years). Diagnosis was based on MICM (morphology, immunology, cytogenetics, and molecular biology) typing standard, and among the patients, 62 cases were acute myeloid leukemia (AML) that was composed of AML-M₀ (1 case), AML-M₁ (8 cases), AML-M₂ (29 cases), AML-M₄ (16 cases), AML-M₅ (6 cases) and AML-M₆ (2 cases), 18 cases were acute lymphoblastic leukemia (ALL), 7 cases were acute hybrid leukemia (AHL), 3 cases were myelodysplastic syndromes and refractory anemia with excess of blasts in transformation (MDS-RAEBt), and 3 cases were AL transformed from MDS (MDS-AL). The patients had no other serious complications involving the major organs before transplantation, and were durable for high-dose radiotherapy and chemotherapy. Patients were regarded with high-risk AL when any of the following conditions applied (14):

(I) Refractory AL; (II) AL beyond the first remission phase; (III) AL with cytogenetic markers for poor prognosis such as positive Philadelphia chromosome (Ph+) and complex karyotype (3 or more chromosomal abnormalities); (IV) MDS-RAEBt or MDS evolving to AL.

Conditioning regimens

Most AML patients received the BAC regimen (busulfan 0.8 mg/kg/q 6 h ×16 doses, cytarabine 2.0-2.5 g ×2 doses and cyclophosphamide 1.8 g/m² ×2 doses; most ALL patients and those with central nervous system leukemia were treated with the TBI + CY regimen (8.0-10.0 Gy total body irradiation and cyclophosphamide 1.8 g/m² daily for 2 days). In a few cases, the regimens were adjusted based on the above classical regimens.

Graft type and stem-cell source

Among the 93 patients, 91 cases underwent PBSCT, and 1 case each received BMT and CD34-selected PBSCT; 60 cases had sibling (related) donor transplantation, and the other 33 cases were transplanted from unrelated donors; 73 cases received human leucocyte antigen (HLA)-matched transplantation, and 20 cases had HLA-unmatched transplantation; 54 cases had ABO compatible donors, and 39 cases were incompatible with their donors.

Prophylaxis and management of GvHD

The prominent regimen for GvHD prophylaxis consisted of cyclosporine A (CsA) and short course of methotrexate, and anti-lymphocyte globulin and mycophenolate mofetil (MMF) were additionally administered in unrelated-HSCT or HLA-unmatched related-HSCT subjects. The treatment regimen for GvHD consisted of CsA, prednisone, and short-term methotrexate, with the addition of tacrolimus, mycophenolate mofetil or monoclonal antibodies depending on the individual's specific condition. The diagnosis and grading of GvHD were done according to established criteria (15), and grade III-IV acute GvHD (aGvHD) was termed severe aGvHD.

Engraftment, chimerism and minimal residual disease detection

Engraftment was defined as the first of 3 consecutive days with white blood cell (WBC) count $\geq 1.0 \times 10^9/L$ and

neutrophil count $\geq 0.5 \times 10^9/L$. Platelet engraftment was defined as the first of 7 consecutive days that the platelet count $\geq 20 \times 10^9/L$ without transfusion support. Chimerism analysis was performed through fluorescent *in situ* hybridization (FISH) studies in sex mismatched cases for Y chromosome, and DNA microsatellite polymorphisms, etc. Minimal residual disease detection was performed by means of FISH, reverse transcriptase PCR, flow cytometry or other methods as appropriate.

Treatment of post-transplant relapse

Treatment of post-transplant relapse was heterogeneous and varied depending on patient's condition, which included immunosuppressant withdrawal, chemotherapy, radiotherapy, intrathecal injection of chemotherapeutic agents, modulating immunity, and donor HSC or lymphocyte infusions.

Statistical analysis

All patients except one were followed up until September 30, 2012. The cumulative incidence of transplantation related mortality (TRM), relapse rate, 3-year overall survival (OS) and 3-year DFS were calculated by Kaplan-Meier method. In univariate analysis, χ^2 test and Fisher's exact test were used to assess differences between the groups, and those variables with P less than 0.10 in univariate analysis were considered for inclusion in multivariate Cox regression models. P values less than 0.05 were considered as statistically significant. All statistical analyses were conducted with SPSS software (version 19.0, SSPS Inc, Chicago, IL).

Results

Hematopoietic reconstitution

The median number of mononuclear cells (MNC) infused was $7.85 \times 10^8/kg$ (range, 5.00×10^8 - $11.70 \times 10^8/kg$) and CD34+ cells infused was $2.80 \times 10^6/kg$ (range, 0.50×10^6 - $7.100 \times 10^6/kg$), respectively. Hematopoietic reconstitution was achieved in 90 patients with an engraftment rate of 96.77%. The medial time to WBC count $> 1.0 \times 10^9/L$ was 13 days (range, 9-15 days) and to neutrophil count $> 0.5 \times 10^9/L$ was 12 days (range, 9-21 days), and to achieve a platelet count $\geq 20 \times 10^9/L$ without transfusion was 16 days (range, 10-35 days) after transplantation, respectively.

Transplant-related complications

The incidence of lung infection within the first 100 days post-transplantation was 43.0%, and the incidence of mixed lung infection (bacteria and fungi) was 26.5%. Six patients with lung infection died. In patients having a history of pulmonary fungal infection before transplantation, the incidence of mixed lung infection within the first 100 days post-transplantation was 50.1%.

Thirty-eight patients developed aGvHD, and 13 cases of them were severe aGvHD with 8 death. Eighty-five patients survived more than 100 days, and chronic GvHD (cGvHD) occurred in 37 cases (43.5%), 17 cases (20%) of whom were extensive cGvHD. As showed by the risk factor analysis, the incidences of severe aGvHD in patients ≥ 40 years of age, and with HLA mismatched grafts or severe lung infection within the first 100 days after transplantation were significantly higher than those in their paired controls (all $P < 0.05$), and the incidences of extensive cGvHD in patients ≥ 40 years of age, with severe lung infection within the first 100 days after transplantation and having a history of severe aGvHD were significantly higher than those in their paired controls (all $P < 0.05$) (Table 1).

Survival, TRM and relapse

The median follow-up period was 26 months (range, 0.1-138 months). At the last follow-up of this study, 63 patients remained alive and 30 patients died. In the entire group of the 93 patients, the 3-year OS and DFS after allogeneic HSCT were $64.6\% \pm 5.4\%$ (95% CI, 55.8-76.4%) and $56.54\% \pm 5.51\%$ (95% CI, 47.2-66.5%), respectively. One AML patient survived for the length of this study (138 months) after transplantation. The 3-year OS and DFS for AML patients were $70.7\% \pm 6.2\%$ (95% CI, 57.6-92.4%) and $61.9\% \pm 6.6\%$ (95% CI, 49.8-72.3%), for ALL patients were $47.4\% \pm 13.7\%$ (95% CI, 35.6-54.9%) and $35.7\% \pm 12.0\%$ (95% CI, 28.7-39.4%), respectively. Of the 7 AHL patients, 2 cases died due to relapse and 1 case died of aGvHD; Of the 6 MDS patients, 1 case each died of relapse and aGvHD.

TRM occurred in 16 patients, of whom, 1 AML patient failed to achieve hematopoietic reconstitution and died 2.5 months after transplantation from a severe pulmonary infection, 2 AML patients died of heart failure during the preparative regimen for transplantation, 7 cases died of severe aGvHD with severe pulmonary infection, 4 cases died of severe pulmonary infection, 1 case died of severe aGvHD, and 1 case died of liver failure. The

Table 1 Analysis of risk factors for GvHD in allogeneic HSCT recipients

Variables	group	Severe aGvHD		Extensive cGvHD	
		Incidence (%)	P value	Incidence (%)	P value
Sex	Male	19.3	0.073	26.0	0.167
	Female	5.6		11.4	
Age (years)	≥40	35.0	0.006	38.9	0.042
	<40	8.2		14.9	
Blood type	Compatible	11.5	0.551	22.9	0.586
	Incompatible	17.1		16.2	
Types of disease	AML	11.3	0.730	21.4	0.535
	ALL	16.7		11.8	
	AHL	0.0		14.3	
	MDS	16.7		40.0	
High risk	Yes	18.8	0.359	22.2	0.775
	No	11.5		19.0	
Related transplantation	Yes	9.7	0.116	18.8	0.823
	No	22.6		21.2	
HLA-matched transplantation	Yes	9.6	0.030	17.1	0.168
	No	30.0		33.3	
Lung infection within first 100 days after transplantation	Yes	41.4	0.000	56.5	0.000
	No	1.6		6.5	
Severe aGvHD	Yes	–	–	90.0	0.000
	No	–		10.7	

3-year cumulative incidence of TRM was 16.8%±6.1% (95% CI, 13.8-17.4%). Univariate analysis indicated that the incidences of TRM in patients ≥40 years, with HLA mismatched graft, severe lung infection within the first 100 days after transplantation, and severe aGvHD were significantly increased versus their paired controls (all $P < 0.05$), while the variables such as sex, blood relationship, type of disease and high-risk AL were not detectably associated with incidence of TRM (all $P > 0.05$).

Twenty-one patients (10 AML, 8 ALL, 2 AHL and 1 MDS-AL) relapsed by the end of follow up, and the 3-year cumulative incidence of relapse was 21.3%±6.7% (95% CI, 18.6-23.5%). Among these patients, 9 cases developed extra-medullary relapse, and 12 cases developed hematological relapse. Six cases of the 9 patients with extra-medullary relapse remitted again and were still alive without disease after radiotherapy, intrathecal injection of chemotherapeutic agents, immunomodulator (IL-2) administration or donor lymphocyte infusion, while the remaining 3 cases died from hematological relapse, and 2 cases of the 12 patients with hematological relapse survived after chemotherapy

and donor lymphocyte or stem cells infusion. Analysis of risk factors for relapse found that patients with high-risk AL or lack of cGvHD had a significantly higher relapse rate compared with their paired controls (both $P < 0.05$), and patients who developed extensive cGvHD presented a lower chance of relapse than those who did not develop this condition, but the difference did not reach statistical significance ($P = 0.102$) (Table 2).

Prognostic factors

The differences among stratified variables in 3-year DFS were analyzed for determination of the risk factors responsible for poor outcomes following allogeneic HSCT. Univariate analysis indicated that HLA mismatch, severe lung infection within the first 100 days post-HSCT, high risk AL, severe aGvHD and lack of cGvHD were associated with unfavorable results, and further multivariate analysis identified that severe lung infection within the first 100 days post-HSCT, severe aGvHD and lack of cGvHD were independent risk factors for poor prognosis (Table 3).

Table 2 Analysis of risk factors for TRM and relapse rate of allogeneic HSCT recipients

Variables	group	TRM		Relapse	
		Incidence (%)	P value	Incidence (%)	P value
Sex	Male	22.8	0.093	15.8	0.074
	Female	8.3		33.3	
Age	≥40	35.0	0.039	15.0	0.547
	<40	12.3		24.7	
Related transplantation	Yes	12.9	0.149	25.8	0.431
	No	25.8		16.0	
Blood type	Compatible	21.2	0.284	17.3	0.214
	Incompatible	12.2		29.3	
HLA-matched transplantation	Yes	12.3	0.039	24.7	0.547
	No	35.0		15.0	
Lung infection within first 100 days after transplantation	Yes	44.8	<0.001	17.2	0.593
	No	4.7		25.0	
Types of disease	AML	17.7	0.996	17.7	0.280
	ALL	16.7		38.9	
	AHL	14.3		28.6	
	MDS	16.7		16.7	
High risk	Yes	18.8	0.779	37.5	0.019
	No	16.4		14.8	
Severe aGvHD	Yes	61.5	<0.001	7.7	0.284
	No	10.0		25.0	
cGvHD	Yes	–	–	10.8	0.020
	No	–		33.3	
Extensive cGvHD	Yes	–	–	6.3	0.102
	No	–		27.5	

Discussion

In this report, we have analyzed 93 patients with AL undergoing allogeneic HSCT over the past 12 years in our hospital. The results showed that the 3-year OS and DFS for the entire group of patients were 64.6%±5.4% and 56.5%±5.5%, for AML patients (with the exclusion of M₃ patients) were 70.6%±6.1% and 61.9%±6.6%, and for ALL patients were 47.4%±13.7% and 35.7%±12.0%, respectively. These results suggested that allogeneic HSCT is an effective treatment modality for patients with AML and ALL as previously reported (3,16-20), but could not draw a significant conclusion for AHL and MDS due to the small number of such cases in this study, which requires verification with a larger sample.

TRM is an important cause of allogeneic HSCT failure (21-23). In our data, the proportion of TRM in the total death-rate was 53.3% (16/30), for which the main causes of death were severe aGvHD and/or serious lung infection

(12/16). As shown in the analyses, age ≥40 years, HLA mismatch, severe lung infection within the first 100 days post-transplant, and severe aGvHD were significantly associated with higher incidence of TRM, and as well, severe lung infection within the first 100 days post-transplant, and severe aGvHD were independent risk factors for poor prognosis of the patients undergoing allo-HSCT. Thus, how to aggressively control severe aGvHD and decrease early lung infection are critical to reducing the incidence of TRM.

As determined by analysis of the relevant factors affecting aGvHD, the incidences of severe aGvHD were increased in patients ≥40 years of age, and with HLA mismatched transplantation or severe lung infection within the first 100 days post-transplantation versus their paired controls (all P<0.05). In our hospital, the incidence of severe lung infection during the first 100 days post-transplantation in patients having a history of pulmonary fungal infection before transplantation was 50.1%, and the mortality rate

Table 3 Analysis of risk factors for poor prognosis of allogeneic HSCT recipients

Variables	group	DFS (%)	P value (Univariate)	P value (Multivariate)
Age	≥40	50.0±11.2	0.2244	–
	<40	58.2±6.7		
Sex	Male	61.74±7.3	0.7457	–
	Female	50.8±8.9		
Related transplantation	Yes	56.2±7.3	0.4191	–
	No	57.4±9.0		
Blood type	Compatible	56.0±7.9	0.8132	–
	Incompatible	55.1±8.4		
HLA-matched transplantation	Yes	59.74±6.3	0.0150	0.116
	No	40.0±12.7		
Lung infection within first 100 days after transplantation	Yes	37.1±9.1	0.0002	0.001
	No	63.9±7.3		
High risk	Yes	33.4±10.7	0.0177	0.085
	No	66.3±6.4		
Severe aGvHD	Yes	30.0±14.5	0.0086	0.040
	No	59.6±6.1		
Extensive cGvHD	Yes	52.9±12.1	0.5430	–
	No	55.9±6.2		
cGvHD	Yes	72.2±7.5	0.0437	0.000
	No	45.8±7.5		

in patients developing severe lung infection was 44.8%, which was only 4.7% in their controls. And not only that, but the incidence of simultaneous severe aGvHD in patients with severe lung infection was high (41.4%). As for the reason, the following three points are considered: (I) Benefits of using massive doses of chemotherapy drugs to reduce the residual tumor cells before transplantation is accompanied with the risk of infection, as evidenced by the increased incidence of severe respiratory infections in recent years. And secondly, patients with pulmonary fungal infection require a long course of therapy, and trend to recur when the immune response decline; (II) Various immunosuppressants are often used for prophylaxis of rejection in patients receiving HLA mismatched transplantation; (III) Infection may elicit GvHD, and the severe aGvHD cases usually require even enhanced immunosuppression, which in turn increases the risk of infections and thereby initiates a vicious circle. Thus, we should fully evaluate the patients to determine the risks and benefits of transplantation, and then to decide whether the transplantation can be done or not, as well as the timing and type of transplantation. Meanwhile, solutions to

eliminate the unfavorable conditions should be introduced as complete as possible before transplantation.

Relapse is another major cause responsible for allogeneic HSCT failure (24,25). In our series, the proportion of death from relapse accounted for 43.3% (13/30) of the total death-rate; patients with high-risk AL or lack of cGvHD had a higher relapse rate compared with their paired controls, while the severe aGvHD, and HLA mismatched or unrelated transplantation provided no benefit for preventing relapse. Furthermore, multivariate analyses identified that lack of cGvHD was an independent risk factor for poor prognosis. GvL is a major beneficial effect of allogeneic HSCT, but it is always closely linked to GvHD. In clinical practice, powerful immunosuppressants are often used for prevention of occurrence of severe GvHD after transplantation, which in turn may compromise the GvL effect and result in an increased relapse rate. Data from our hospital showed that the relapse rate in patients experienced cGvHD was significantly lower than in those without cGvHD (10.8% *vs.* 33.3%, $P < 0.05$), and patients with extensive cGvHD also had a lower chance of relapse than those without this condition but no statistical

significance was reached (6.3% *vs.* 27.5%, $P > 0.05$), and this fact indicates that the limited GvHD offers the advantages of not only reducing relapse but also improving quality of life of allogeneic HSCT patients. So, the treatment plans for the patients should be gradated and individualized. And in patients with high-risk factors, both dose and course of immunosuppressive drugs should be reduced as much as possible on the basis of severe aGvHD prophylaxis, and immunoregulatory measures such as immunomodulator regimens and donor lymphocyte infusion should be implemented as early as possible to induce moderate GvHD which produces the GvL effect.

In conclusion, allogeneic HSCT is the main and even the only choice for treatment of AL, and whether there is therapeutic benefit depends on the comprehensive assessment for the disease severity and potential risks associated with transplantation. Further development and improvement of HSCT techniques along with gradated and individualized therapy are expected to provide better outcomes and improved quality of life for AL patients.

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