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Hematopoietic Stem Cell Transplantation for Treatment of Patients with Leukemia Concomitant with Active Tuberculosis Infection

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Background: Currently, hematopoietic stem cell transplantation is still an essential treatment approach for leukemia. However, patients with leukemia often have weakened immune function, especially more seriously compromised cellular immune response, and appear to be at greater risk for tuberculosis infection during the transplantation process. We aimed to investigate the efficacy and safety of hematopoietic stem cell transplantation for the treatment of patients with leukemia accompanying active tuberculosis infection.

Material/Methods: We retrospectively analyzed records of 7 consecutive patients who were diagnosed with leukemia concomitant with active tuberculosis infection and who underwent hematopoietic stem cell transplantation in our hospital from January 2006 to December 2012.

Results: Among these 7 patients (4 males and 3 females; median age: 38 years; range: 30–46 years), the mean duration of anti-TB treatment before transplantation was 3 months (range: 2–4.5 months). All patients acquired engraftment, with an implantation rate of 100%. After transplantation, the mean duration of anti-TB treatment was 12 months. All patients had response after receiving anti-TB treatment. One patient died of leukemia relapse 6 months after the transplantation, but no tuberculosis infection-related death was reported.

Conclusions: Patients with leukemia concomitant with active tuberculosis infection can be treated with hematopoietic stem cell transplantation if they receive an effective anti-TB treatment regimen. The anti-TB treatment regimen had no effect against hematopoietic stem cell transplantation and was well-tolerated. All post-transplanted patients experienced no relapse of tuberculosis during the immune-suppression period. The findings in the present investigation deserve further in-depth study.

MeSH Keywords: Adult Stem Cells • Leukemia, Biphenotypic, Acute • Mycobacterium Tuberculosis

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Background

The immune response in patients with leukemia is significantly lower than that in the healthy population, which makes patients more susceptible to bacterial, viral, fungal, or other infections. With the rising incidence of tuberculosis in recent years, the number of patients with leukemia concomitant with tuberculosis is gradually growing. Researchers demonstrated that the incidence of leukemia concomitant with tuberculosis varies from center to center, for example,2.3% reported by Silva in Brazil [1], 2.0% reported by Al-Anazi in Saudi Arabia [2], 2.0% reported by Chen in Taiwan China [3], and 1.2–8.3% in China [4]. The difference in incidence can be explained by the difference in sample size and tuberculosis-endemic regions.

The mechanism for increased risk of developing tuberculosis in patients with leukemia has been studied by some scholars. Caver et al. [5] reported that the decrease in CD4-positive cells and the ratio of CD4 + to CD8 +, relative increase in CD8 + but with functional decline in patients with acute leukemia and bone marrow suppression in the initial visit or after chemotherapy might contribute to a high incidence of tuberculosis in patients with leukemia. Silva et al. proposed that risk factors for patients with hematologic malignancies and concomitant tuberculosis included poor nutrition and administration of fludarabine or corticosteroids, and high-risk factors included hematologic malignancy type and treatment regimen leading to significantly impaired T cell-mediated immunity (e.g., Hodgkin's lymphoma, adult T-cell leukemia/lymphoma, and high-dose corticosteroids or fludarabine therapy for patients undergoing hematopoietic stem cell transplantation or with lymphoproliferative disorders) [1].

Hematopoietic stem cell transplantation is still one of the most effective therapies to eradicate leukemia. There are no cases of leukemia with active tuberculosis receiving hematopoietic stem cell transplantation previously reported in the literature. In this report, we analyzed 7 patients with leukemia accompanying active tuberculosis who underwent hematopoietic stem cell transplantation, in order to investigate the efficacy and safety.

Material and Methods

Patients group

Between January 2006 and December 2012, 7 out of 65consecutive patients who were diagnosed with leukemia concomitant with active TB in our hospital and who underwent hematopoietic stem cell transplant were included in the study. Patients with leukemia, including acute and chronic leukemia, were diagnosed according to FAB criteria and with concomitant tuberculosis if any of the following condition was met: chest X-ray or CT scan revealed typical pulmonary tuberculosis; patients had positive TB skin test; acid-fast bacilli was detected in sputum smears.; patients had fever for over 2 weeks, or had no response to antibacterial and -fungal therapy but had response to anti-TB therapy.

Inclusion and exclusion criteria

Patients who were diagnosed with leukemia accompanying tuberculosis in the process of the study or accompanying onset of tuberculosis in the course of leukemia treatment while undergoing hematopoietic stem cell transplantation were included, excluding those who presented with inactive pulmonary tuberculosis in the process of leukemia treatment, were diagnosed with tuberculosis before diagnosis of leukemia, or were diagnosed with leukemia accompanying HIV or other malignancies.

Anti-TB regimen

After the diagnosis of tuberculosis, patients received standard triple (isoniazid, rifampicin, ethambutol or pyrazinamide) or quadruple anti-TB regimen (isoniazid, rifampicin, pyrazinamide, streptomycin or ethambutol) at standard doses [6]. Patients received second-line drugs (moxifloxacin and amikacin) instead of oral anti-TB drugs during the transplantation, and continued with the original triple or quadruple anti-TB regimen after recovery of hematopoietic function after transplantation. All patients signed informed consent.

Transplantation approach and conditioning regimen

Of the 7 patients in the study, 5 underwent HLA-identical sibling peripheral blood stem cell transplantation, 1 underwent autologous peripheral blood stem cell transplantation, and 1 underwent autologous bone marrow transplantation. The standard CY/TBI were employed as the transplant conditioning regimen. CsA + MTX were used for prevention of GVHD during allogeneic transplantation.

Efficacy endpoint and follow-up

During and after the transplantation, attention should be given to adverse effects caused by anti-TB drugs, especially to the relapse of leukemia and the resurgence of tuberculosis after discontinuation. Regular monitoring of liver and kidney function, detection of minimal residual levels of leukemia in bone marrow, and lung CT scan were performed during the study. All patients were followed up for 12 months after transplantation and then assessed. The signs, including negative sputum, decrease or disappearance of tuberculosis, improvement in clinical symptoms, and radiographic improvement, were defined as "response" or otherwise as "non-response" [6].

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Table 1. Characteristics of patients with TB disease.

Patient No.	Sex	Primary disease	Tuberculosis	PPD	TB-Ab test	AFB	TB culture	E-LISPOT	Imaging examination	Outcome
1	M	AML-M2	TB	+	Negative	Negative	Negative	Negative	Fibrous stripes	Response
2	M	AML-M4	TB	+	Negative	Negative	Negative	Positive	Nodules	Response
3	M	B-ALL	TP	+++	Positive	Negative	Negative	Positive	Pleural effusion	Response
4	F	CML	TB	++	Negative	Negative	Negative	Negative	Nodules	Response
5	M	AML-M7	TB	+++	Positive	Negative	Negative	Positive	Fibrous stripes	Response
6	F	B-ALL	TB	++	Negative	Negative	Negative	Negative	Nodules	Response
7	F	CML	TB	++	Negative	Negative	Negative	Negative	Nodules	Response

Results

Anti-tuberculosis treatment in patients

Seven out of 65 consecutive patients who had been diagnosed with leukemia accompanying active TB within 6 years in our hospital received hematopoietic stem cell transplantation. These 7 patients comprised 4 males and 3 females, with a mean age of 38 years (range: 30–46 years). Regarding primary disease, there were 3 cases of acute myeloid leukemia (1 with AML-M2, 1 with AML-M4, and 1 with AML -M7), 2 cases of acute lymphoblastic leukemia (ALL), and 2 cases of chronic myelogenous leukemia (CML).

All 7 patients had cough, sputum, night sweats, weight loss, and other symptoms of tuberculosis, of which 4 showed typical radiographic findings of tuberculosis, 3 had positive tuberculosis antibody test results and had no response to anti-bacterial therapy and were diagnosed with tuberculosis, and 1 developed positive pleural effusion for antinuclear antibody. Before transplantation, the patients received regular triple or quadruple anti-TB regimen for an average of 3 months. After treatment, all patients showed response, including improved cough and sputum symptoms and gradual absorption of tuberculosis, but did not achieve complete response. Patients received intravenous injection of moxifloxacin and amikacin instead of oral anti-TB drugs during the transplantation, and could not continue with the original regimen until recovery of hematopoietic function after transplantation. The quadruple anti-TB regimen was replaced by a double anti-TB regimen 6 months after the transplantation, and then anti-TB drugs were completely discontinued 1 year after transplantation. One patient with AML-M7 required long-term immunosuppressive drug treatment as a result of extensive cGVHD after transplantation, and received 2.5 years of anti-TB treatment until the lung lesions became completely absorbed. Characteristics of patients with TB disease are shown in Table 1.

Overview of transplantation in patients

Seven patients with leukemia presented with complete response before transplantation, and showed active hyperplasia in bone marrow 30 days after transplantation and completion response of leukemia. All patients were full-donor chimeras. Median neutrophil engraftment time was 16 days (range: 12–45 days) and 17 days (range: 12–60 days) for platelets.

After transplantation, there were 3 cases of grade II skin aGVHD and 2 cases of extensive cutaneous cGVHD among patients undergoing allotransplantation, all of which disappeared by improving immunosuppression. During the 12-month follow-up period, all the patients showed complete response, except 1 patient with ALL who died of leukemia relapse 6 months after transplantation and the other patient with AML-M7 who experienced relapse of leukemia 5 months after transplantation and achieved complete response after receiving chemotherapy again with donor lymphocyte infusion twice, and remained in complete response till the last follow-up. Characteristics of transplantation are shown in Table 2.

Discussion

The risk of hematopoietic stem cell transplantation appears to be increased among patients with leukemia accompanying TB, as the re-activation of tuberculosis may occur in the process of transplantation as a result of extremely low immune response.

The diagnosis of latent tuberculosis infection is recommended in hematological malignancy patients and before hematopoietic stem cell transplantation. It has been suggested that the T-SPOT.TB is useful for screening tuberculosis infection in hematological malignancy patients and hematopoietic stem cell transplant recipients [7].

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Table 2. Characteristics of transplantation in patients.

Patient No.	Sex	Primary disease	Transplantation approach	Conditioning regimen	Neutrophil engraftment	Platelet engraftment	Acute GVHD	Chronic GVHD	Follow-up
1	M	AML-M2	Auto	CY/TBI	30	60	None	None	12+
2	M	AML-M4	Auto	CY/TBI	45	55	None	None	12+
3	M	B-ALL	Identical sibling	CY/TBI	17	17	None	None	Died of relapsed leukemia 6 months later
4	F	CML	Identical sibling	CY/TBI	16	20	Grade 2	Extensive skin involvement	12+
5	M	AML-M7	Identical sibling	CY/TBI	14	16	Grade 2	Extensive skin involvement	12+
6	F	B-ALL	Identical sibling	CY/TBI	12	12	None	None	12+
7	F	CML	Identical sibling	CY/TBI	15	15	Grade 2	None	12+

Co-morbid opportunistic infections, profound host immunosuppression early after transplantation, and potential risk of multi-drug resistant TB may act as major barriers to effective treatment of tuberculosis after hematopoietic stem cell transplantation, despite appropriate anti-TB medication [8]. Among these 7 cases of leukemia concomitant with active tuberculosis undergoing hematopoietic stem cell transplantation in this present report, no case of tuberculosis infection-related death was found. Tuberculosis is not obviously exacerbated during the transplantation, indicating that the patients with leukemia accompanying active TB can be accepted for allogeneic hematopoietic stem cell transplantation based on the following conditions:

The regular, concomitant, and properly extended anti-TB regimen is administered to patients. Patients with leukemia concomitant with tuberculosis receiving the triple or quadruple anti-TB regimen comprised of first-line drugs at standard dose without interfering with chemotherapy achieved response rate up to 80% [9,10]. In the present study, a 100% response rate was reported in 7 patients who initially received standard triple or quadruple anti-TB regimen. Yuen et al. [11] proposed a 1-year quadruple drug regimen for the first half of the year, followed by a double or triple drug regimen for the second half of the year, based on the treatment regimen for immunocompromised patients. Generally, patients showed good response to anti-TB treatment without relapse after discontinuation of treatment, suggesting that secondary prevention after immune reconstitution was unnecessary. In our study, the regular triple or quadruple drug anti-TB regimen was administered to 7 patients with tuberculosis upon diagnosis, and was replaced by second-line anti-TB drugs – moxifloxacin and etimicin – due to the bone marrow suppression, liver and kidney toxicity, and other adverse effects of oral anti-TB drugs, so as to ensure the adverse effects did not affect the transplantation process, and the regular regimen was resumed after engraftment of hematopoietic granulocytes. The tuberculosis was not obviously exacerbated in 7 patients with bone marrow suppression after transplantation, indicating that hematopoietic stem cell transplantation was safe for patients with leukemia accompanying TB that had been effectively controlled. The second-line anti-TB drugs, moxifloxacin and etimicin, were effective in controlling tuberculosis infection without affecting hematopoietic reconstruction. One patient with M7 required long-term immunosuppressive drugs due to extensive cGVHD after transplantation, and received 2.5 years of anti-TB treatment until the lung lesions became completely absorbed, in whom TB treatment was well tolerated without causing any obvious liver and kidney toxicity.

Regular chemotherapy without reduction in dose should be administered to patients with leukemia who are receiving anti-TB regimen simultaneously. It was demonstrated that leukemia chemotherapy was not affected by tuberculosis and tuberculosis was not aggravated during the chemotherapy process [10], implying that patients with leukemia accompanying tuberculosis might be treated with a standard leukemia regimen. In the present report, 7 patients received simultaneous treatment for leukemia and TB, and underwent hematopoietic stem cell transplantation for leukemia after achieving complete response in leukemia. No drug dosage adjustment was made to chemotherapy and transplant conditioning regimens in order to eradicate leukemia, indicating that patients with tuberculosis were allowed to undergo chemotherapy and transplantation at the standard dose.

Conclusions

Based on the information available, it can be concluded that hematopoietic stem cell transplantation is safe and effective for patients with leukemia accompanying active tuberculosis if

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they are treated with effective anti-TB regimen without interfering with the transplantation and under close observation with timely dose adjustment. Because of limited sample size, larger-scale studies are needed to more fully explore these findings.

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