

Tuberculosis before hematopoietic stem cell transplantation in patients with hematologic diseases: report of a single-center experience

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Transpl Infect Dis 2015; **17**: 73–79. All rights reserved

Abstract: *Background.* Few reports discuss the optimal management of patients diagnosed with tuberculosis (TB) before scheduled stem cell transplantation (SCT), who then proceed with transplantation.

Methods. We found 13 patients with TB before SCT (proven, $n = 9$; probable, $n = 3$; possible, $n = 1$) in the medical records of our institution.

Results. Most of the patients had pulmonary TB ($n = 8$; disseminated, $n = 2$; extrapulmonary, $n = 3$). Eight of 9 patients with proven disease had SCT after at least 100 days of anti-tuberculous medication, ranging from 103 to 450 days. None of those patients suffered TB-related events after SCT. However, 1 patient with proven pulmonary TB who underwent SCT after only 40 days of anti-tuberculous therapy subsequently died of TB meningitis. Patients with possible and probable disease had their transplants after 6–176 days of anti-tuberculous medication, and all were alive at the time of analysis. The entire duration of anti-tuberculous medication was 12 months in most cases. With a follow-up duration ranging from 0.7 to 87.5 months, 4 patients died, but TB was the cause of death in only 1 case.

Conclusion. In conclusion, for proven cases of TB, SCT after >100 days of anti-tuberculous medication is probably feasible and safe, in terms of TB control, in patients with various hematologic diseases.

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Key words: tuberculosis; hematologic diseases; stem cell transplantation

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Received 20 August 2014, revised 9 October 2014, accepted for publication 22 November 2014

DOI: 10.1111/tid.12341

Transpl Infect Dis 2015; **17**: 73–79

Abbreviations: AFB, acid-fast bacilli; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATG, anti-thymocyte globulin; Bu, busulfan; CMV, cytomegalovirus; CSF, cerebrospinal fluid; Cy, cyclophosphamide; Flu, fludarabine; GVHD, graft-versus-host disease; MC, myeloablative conditioning; Mel, melphalan; RIC, reduced-intensity conditioning; SAA, severe aplastic anemia; SCT, stem cell transplantation; TB, tuberculosis; TBI, total body irradiation

The incidence of tuberculosis (TB) might be particularly high in patients with hematologic malignancies, because of T-cell immunodeficiency caused by the underlying disease, or the administration of cytotoxic chemotherapy and high-dose corticosteroid therapy (1–3). The prevalence and mortality of TB in hematologic

malignancies is high, reported at between 0.72% and 2.6% (4) and approximately 17% (5) respectively. In addition, TB is still a problem in South Korea, where its overall incidence remains in the intermediate range (6, 7) (73 cases per 100,000 persons in 2005), although the prevalence decreased in the period from 1965 to 1995 (940 down to 219 cases per 100,000 persons) (8, 9).

Stem cell transplantation (SCT) is a curative treatment modality and plays a critical role in the treatment of many hematologic malignancies and bone marrow failure conditions, such as leukemia, severe aplastic anemia (SAA), and myelodysplastic syndrome. However, SCT causes severe impairment of immunity, as a result of the conditioning used, immunosuppressive therapy, and graft-versus-host disease (GVHD) (10, 11). Accordingly, transplant recipients are susceptible to reactivation or progression of pre-existing TB. As far as we know, few data are available regarding optimal management of TB in patients with hematologic disease who need SCT. Herein, we report the successful outcome of anti-tuberculous treatment for adult patients who developed TB before SCT.

Patients and methods

Study design and patients

We reviewed the medical records of patients who received SCT at the Catholic Blood and Marrow Transplantation Center between January 2004 and December 2013, and analyzed the outcomes. During this period, a total of 3061 transplants were performed, 2841 of them in adult patients. Among these, we identified 13 adult patients who developed TB before SCT and were treated with anti-tuberculous medication. This study was approved by the Institutional Review Boards of Seoul St Mary's (8 patients) and Yeouido St Mary's Hospitals (5 patients).

Definitions

The categories of TB were described in our previous study (12, 13). Briefly, TB was classified as "proven" if *Mycobacterium tuberculosis* was cultured from any clinical specimen. The diagnosis of a "probable" case of TB required at least one of the following criteria in patients with clinical symptoms and signs suggestive of TB: (i) acid-fast bacilli (AFB) seen in a clinical specimen (sputum, body fluid, etc.); (ii) pathologic finding suggesting TB, such as caseous necrosis with or without granuloma (including positive Ziehl-Neelsen stain); or

(iii) body fluid analysis (pleural or pericardial effusion, ascites, or cerebrospinal fluid [CSF]) showing lymphocyte predominance and high adenosine deaminase (>40 IU/L, or >10 IU/L in CSF), when the patient had no evidence of malignancy. The "possible" TB category included patients with clinical or radiologic response to empirical anti-tuberculous treatment with positive interferon- γ -releasing assay. Polymerase chain reaction for TB was used only to distinguish TB from non-tuberculous mycobacterial infection, not for determining TB diagnosis or activity. Sensitivity tests for anti-tuberculous drugs were performed using Löwenstein-Jensen media and the absolute concentration method. Anti-tuberculous medication consisted of 2 months of isoniazid, rifampin, ethambutol, and pyrazinamide, followed by isoniazid, rifampin, and ethambutol for the rest of the treatment period. Treatment could be modified by culture susceptibility and was followed up by an infectious diseases specialist. Since 2011, we changed rifampin to rifabutin at the time patients began to take immunosuppressants during the transplantation procedure. If aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) increased to >5 times the upper normal limit, we immediately changed first-line hepatotoxic anti-tuberculous medication to less hepatotoxic second-line medication, and restarted as soon as the AST and/or ALT dropped to 2–3 times the normal range, one medication at a time, starting from isoniazid at the lowest dose. Drug level of immunosuppressants was monitored twice weekly before discharge and then reevaluated on patient's visits. Decision on the duration of anti-tuberculous medication was based on the physician's preference, but treatment usually lasted 12 months. All patients with "proven" TB proceeded to SCT after confirmation of negative conversion of the culture or AFB smear, and resolution of clinical symptoms and/or radiologic findings before SCT. Patients with "probable" and "possible" TB had SCT after confirming clinical and/or radiologic improvement of the infection.

Transplantation procedure

The SCT procedures were as follows: for hematologic malignancies, the myeloablative conditioning (MC) regimens consisted of high-dose total body irradiation (TBI) (range, 1200–1320 cGy) and cyclophosphamide (Cy) (120 mg/kg). The non-TBI MC regimen used busulfan/Cy (Bu/Cy). Reduced-intensity conditioning (RIC) regimens were all fludarabine (Flu)-based, i.e., Flu/intravenous (IV) Bu or melphalan (Mel) \pm low-dose TBI (Flu/Bu or Mel \pm TBI, 800 cGy). The

combination of TBI, Ara-C, and Mel was the conditioning regimen for autologous SCT. To treat SAA with SCT from a matched sibling donor, the combination of a reduced dose of Cy (100 mg/kg IV), anti-thymocyte globulin (ATG) (10 mg/kg IV, rabbit type; IMTIX-Sangstat, Lyon, France), and Flu (180 mg/m² IV) was used as a conditioning regimen. To treat SAA with SCT from an unrelated donor, TBI (800 cGy) plus Cy was used. The prophylactic regimen for GVHD was a combination of cyclosporine and short-term methotrexate. Granulocyte-colony stimulating factor was administered to all patients at a dose of 5 mg/kg per day subcutaneously from day 7 after the transplant until neutrophil recovery. The other general transplantation procedures were performed as described in previous reports (14, 15). During the SCT, all patients received oral ciprofloxacin (500 mg twice a day) and itraconazole oral solution (200 mg twice a day) or micafungin (50 mg daily) from the first day of conditioning until engraftment. Trimethoprim-sulfamethoxazole (1 single-strength tablet daily) was administered for *Pneumocystis jirovecii* prophylaxis after engraftment until discontinuation of the immunosuppressant therapy. Patients also received herpes simplex virus prophylaxis with acyclovir (400–800 mg orally twice a day or 5 mg/kg IV, 3 times a day) from day 7 to engraftment for transplants from matched-related donors. Patients who underwent allogeneic SCT from mismatched-related donors or unrelated donors received high-dose IV acyclovir (10 mg/kg 3 times a day) for cytomegalovirus (CMV) prophylaxis until engraftment. To prevent CMV disease, preemptive therapy was conducted in a CMV DNA load-guided, risk-adapted manner. Management of neutropenic fever during the peritransplant period has been described elsewhere (16).

Results

Patient characteristics are described in Table 1, and detailed treatment outcomes are summarized in Table 2. The 13 cases included 8 male and 5 female patients between 25 and 59 years of age (median age 47 years). Acute myeloid leukemia was the most common underlying disease ($n = 6$), including 1 patient with secondary acute myeloid leukemia evolving from myelodysplastic syndrome. Most patients had pulmonary TB ($n = 8$), but 2 patients presented with disseminated disease (prostate/liver/spleen and lung/spleen, respectively) and 3 had extrapulmonary disease (cervical lymph node in 1, liver disease in the 2 others).

Duration of anti-tuberculous treatment before SCT was a median of 139 days (range, 6–450 days). By our

Demographic characteristics of patients with tuberculosis (TB) before stem cell transplantation (SCT)

Characteristic	$n = 13$
Gender, male/female	8/5
Age, years, median (range)	47 (25–59)
Diagnosis, n	
AML	6
ALL	1
MPAL	1
MDS	3
SAA/VSAA	1/1
Intensity of conditioning, n	
Myeloablative	7
Reduced intensity	6
Type of SCT, n	
Allogeneic	12
Autologous	1
Donor type, n	
Related	6
Unrelated	6
HLA matching, n	
Fully matched	8
Mismatched	2
Haploidentical	2
Duration of anti-TB medication prior to SCT, days, median (range)	139 (6–450)
Addition of ATG to conditioning regimen, n	
Yes	7
No	6

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MPAL, multi-phenotype acute leukemia; MDS, myelodysplastic syndrome; SAA, severe aplastic anemia; VSAA, very severe aplastic anemia; HLA, human leukocyte antigen; ATG, anti-thymocyte globulin.

Table 1

definition, 9 patients had proven TB, 1 had probable TB, and 3 patients had possible TB. The total duration of anti-tuberculous medication was 12 months for all patients except 1 (Patient 3), who was treated for 6 months. For patients with acute leukemia ($n = 7$), TB developed before the institution of remission-induction chemotherapy in 4 patients, and the remaining patients developed TB during treatment (induction and consolidation chemotherapy).

SCT was undertaken safely in most cases. Eight of 9 patients with proven TB had SCT after at least 100 days

Clinical characteristics and outcomes in stem cell transplantation (SCT) recipients diagnosed with tuberculosis (TB) before SCT

Pt. No.	Gender/ age, years	Diagnosis	Type of SCT/donor source	Preparative regimen	Duration from TB treatment to SCT (days)	Category of TB	Site of TB	Sensitivity test	Outcome/Cause of death, duration of follow-up (months)
1	F/25	MPAL	R/HM	TBI/Cy	40	Proven	Lung	N/A	Died/TB meningitis, 2.6
2	M/37	ALL	U/MM	Flu/Mel + ATG	176	Possible	Lung	N/A	Alive in CR, 87.5
3	M/42	AML	R/HM	TBI 1320/Cy	134	Proven	Lung	S	Alive in CR, 83.7
4	F/34	VSAA	U/HM	TBI 800/Cy	6	Possible	Liver	N/A	Alive in CR, 66.6
5	F/52	AML	U/HM	TBI 1200/Cy	273	Proven	Lung	S	Died/ <i>Pneumocystis jirovecii</i> pneumonia, 4.2
6	M/41	MDS	U/MM	Flu/Bu + ATG	153	Proven	Disseminated (Prostate/ Liver/Spleen)	S	Alive in CR, 42.9
7	M/53	AML	U/HM	TBI 1320/Cy	103	Proven	Disseminated (Lung/Spleen)	S	Died/Sepsis (<i>Stenotrophomonas maltophilia</i>), 0.7
8	M/48	Secondary AML	R/HI	Flu/Bu/TBI 800 + ATG	27	Possible	Liver	N/A	Alive, disease relapse, 10.0
9	M/30	SAA	R/HM	Flu/Cy + ATG	139	Proven	Lung	S	Alive in CR, 37.0
10	M/56	MDS	R/HM	Flu/Bu + ATG	450	Proven	Lung	S	Died/disease relapse, 15.5
11	F/59	AML	R/HI	Flu/Bu/TBI 800 + ATG	215	Proven	Lymph node (cervical)	INH R	Alive in CR, 7.2
12	M/53	AML	U/HM	Bu/Cy + ATG	348	Proven	Lung	S	Alive in CR, 7.2
13	F/47	AML	Autologous /NA	TAM	98	Probable	Lung	N/A	Alive, disease relapse, 5.6

Pt. No., patient number; F, female; MPAL, multi-phenotype acute leukemia; R, related; HM, HLA matched; TBI, total body irradiation; Cy, cyclophosphamide; N/A, not available; M, male; ALL, acute lymphoblastic leukemia; U, unrelated; MM, HLA mismatched; Flu, fludarabine; Mel, melphalan; ATG, anti-thymocyte globulin; CR, complete remission; AML, acute myeloid leukemia; S, sensitive to all drugs; VSAA, very severe aplastic anemia; MDS, myelodysplastic syndrome; Bu, busulfan; HI, haploidentical; SAA, severe aplastic anemia; INH R, resistant to isoniazid; NA, not applicable; TAM, TBI + Ara-C + melphalan.

Table 2

of anti-tuberculous treatment, ranging from 103 to 450 days (median 184 days). Among proven cases, susceptibility results were obtained in 8 patients (all isolates were susceptible against rifampin, and only 1 isolate was resistant to isoniazid; Table 2).

With a follow-up duration ranging from 0.7 to 87.5 months, 4 patients died overall, but only 1 death was TB related (Patient 1). This patient was diagnosed with multi-phenotype acute leukemia, and pulmonary TB was proven during consolidation chemotherapy. After treatment with anti-tuberculous medication for 40 days, the patient received an allograft from her matched sibling donor after MC. ATG was not added to the conditioning regimen. At day 63 after SCT, she

developed sudden eyeball deviation, and the findings on brain magnetic resonance imaging suggested TB meningitis with parenchymal involvement. No AFB was identified on the smear, and there was no growth of microorganism, including *Mycobacterium* species, in the CSF. Sugar and protein levels in the CSF were 95 mg/dL (reference range, 40–70 mg/dL) and 85.5 mg/dL (reference range, 15–45 mg/dL) respectively. However, because no drug sensitivity test was performed for this patient, it is uncertain whether the treatment failure resulted from reactivation of TB or resistant TB, which remains a limitation on the analysis of outcome for this patient. She died of TB meningitis 78 days after SCT. In the remaining

patients, no TB reactivation or TB-related events were observed.

Of the 4 patients who died, 2 patients (Patients 5 and 7) succumbed to infectious diseases, *Pneumocystis jirovecii* pneumonia and *Stenotrophomonas maltophilia* bacteremia, respectively, suggestive of their profoundly immunosuppressed status. The last patient had a relapse of the underlying disease at 390 days post transplant and died of subsequent pneumonia. Four patients without proven TB (possible, $n = 3$, probable, $n = 1$) proceeded to SCT after anti-tuberculous medication for 6–176 days (median 62.6 days). None of them experienced reactivation of TB or TB-related complications.

Two patients had disseminated TB at the time of diagnosis. They were diagnosed with miliary pulmonary nodules and accompanying multiple extrapulmonary lesions (liver, spleen, and prostate in 1 patient, and splenic micro-abscesses with lung involvement in the other patient). They received SCT after anti-tuberculous treatment for 103 and 153 days respectively. One patient (Patient 7), with disseminated TB, died of a condition other than TB (*S. maltophilia* bacteremia) during the pre-engraftment period, and the other patient (Patient 6) safely underwent SCT after RIC, consisting of Flu, Bu, and ATG (10 mg/kg), and is alive and in complete remission 42.9 months post transplant. ATG was used in 7 patients to prevent GVHD, and none of them experienced reactivation of TB post transplant.

In our study, 6 patients were transplanted since 2011 and they received rifabutin instead of rifampin after commencing immunosuppressants. Two patients suffered significant hepatotoxicity; their AST and/or ALT level increased >5 times the upper limit. Because it is often difficult to differentiate the hepatotoxicity caused by anti-tuberculous medication from the toxicities of the conditioning regimen, other medications used during the transplant procedure, or even from hepatic GVHD, sometimes we observed for a change in the transaminase level, without any modification of anti-tuberculous medication, despite the significant hepatotoxicity. For Patient 1, the transaminase level dropped soon, without modification of anti-tuberculous medication. Patient 2 required modification of the medication; levofloxacin was substituted for isoniazid, rifampin, and pyrazinamide. We waited for the reduction of transaminase level to 3 times the normal range and restarted with isoniazid at the lowest dose. No significant elevation in the transaminase level recurred in Patient 2. Two other patients experienced AST/ALT elevation, but to <5 times the normal range; elevation was transient, and resolved spontaneously. We checked the drug level of immunosuppressant twice a week

during the transplantation period before discharge of the patients. Two patients experienced a significant drop in the drug level, and modification of the dosage was required, but did not alter transplant outcomes.

Discussion

Until now, the optimal duration of anti-tuberculous medication for patients with hematologic malignancy or bone marrow failure who become infected with TB before SCT, and when best to proceed to SCT in those patients, have been largely unknown. The standard short-course anti-tuberculous drug regimen (i.e., a 2-month initiation phase with a 4-drug combination [isoniazid, rifampin, ethambutol, pyrazinamide], followed by a 4-month continuation phase with isoniazid and rifampin) is recommended for most cases in the transplant setting, particularly for severe and/or disseminated forms of TB. Based on expert opinion, the continuation phase could be extended to 7 months in patients with pulmonary TB and cavitation on the initial chest radiograph, or if sputum cultures remain positive after 2 months of treatment, as those patients have a higher rate of relapse (17). However, direct evidence to support management of those patients is lacking, and largely depends on expert opinion and extrapolation from immunocompetent and other immunocompromised populations (18). Furthermore, no direct references were made to pre-SCT management of TB and the duration of anti-tuberculous medication. In general, patients should have at least 2 months of induction treatment, and it is preferred, although not always possible, to complete the full treatment against TB before SCT (evidence level D) (18).

In our study, patients with proven TB safely underwent SCT after at least 100 days (range 103–450 days, median 184 days) of anti-tuberculous medication, except for 1 patient. The early transplant recipient (duration of anti-tuberculous medication before SCT was only 40 days) succumbed to radiologically identified TB meningitis with parenchymal involvement after SCT. Our study suggests that, at least for patients with proven TB, >100 days of pre-SCT anti-tuberculous treatment would be a reasonable management option after microbiologic, radiologic, and clinical improvement in TB are achieved. The good prognosis might have been a result of the fact that most of the proven cases were susceptible to isoniazid and rifampin (7 of 9 proven TB). The patients with possible or probable TB proceeded to SCT in 6–173 days of anti-tuberculous medication, resulting in successful outcomes, in terms

of controlling TB. Significant hepatotoxicities were observed in 2 patients; however, only 1 patient needed modification of post-SCT anti-tuberculous treatment. Another 2 patients showed low immunosuppressant drug level, requiring an increase of the drug dosage, without altering the transplant outcomes.

TB treatment in SCT recipients is known to differ from that in the general population in several ways. First, because rifampin interacts with immunosuppressive drugs from the calcineurin inhibitor family (cyclosporine and tacrolimus), rapamycin, and corticosteroids (19–22), rifampin-sparing treatment regimens are preferred by many physicians. If rifampin is used, the risk of rejection may be increased owing to lowered levels of calcineurin inhibitors; consequently, levels of cyclosporine or tacrolimus should be carefully monitored and doses should be adapted (3–5-fold increase) (22). Second, adverse drug events are more frequent. Consequently, one or more first-line drugs cannot be used, and thus the recommended duration of therapy could be longer than in the general population (23–25). Furthermore, it is often difficult to discriminate adverse drug events from GVHD. The length of treatment and the drugs used after the first 2 months are controversial areas, especially if rifampin is not used in the first 2 months or must be suspended because of intolerance. Third, as no consensus or guideline exists on how long these patients should be treated with anti-tuberculous medication, the duration might be prolonged and should be individualized, depending on several factors, such as whether the patient takes immunosuppressants. Most of our patients were treated with a 10-month continuation phase, but it is uncertain whether this extension is required, which warrants further investigation. Anti-tuberculous treatment was tolerable, and the combination of 4 anti-tuberculous medications for the first 2 months was feasible in most of our patients.

Two patients had disseminated TB in miliary form. Miliary TB has been regarded as a disease with poor prognosis, given that mortality from the disease has remained high, in spite of effective treatment. Several predisposing or associated factors describe patients with miliary TB: childhood infection, malnutrition, human immunodeficiency virus infection, alcoholism, diabetes mellitus, chronic kidney disease, dialysis, gastrectomy, organ transplantation, connective tissue disorders, pregnancy or near-term postpartum, presence of an underlying malignancy, and silicosis (26). Although SCT is associated with these predisposing factors, the patients with miliary TB in our study did not suffer reactivation of miliary TB. Although our experience is quite limited, SCT might be undertaken safely

for patients with miliary TB, as long as the disease is controlled and sufficient treatment duration is provided before SCT.

Because cellular immunity, which is the main factor in controlling TB, is markedly impaired post transplant, SCT is also likely to reactivate TB. The MC regimen is known to be associated with more profound immunosuppression and delayed immune reconstitution, compared with RIC, suggesting that patients given MC are more prone to develop TB reactivation. Of the 7 patients who received MC, 1 patient (Patient 1) succumbed to TB reactivation. However, we attribute this reactivation to the short duration of pre-SCT anti-tuberculous treatment (40 days), rather than to the conditioning intensity, given that the remaining patients with a sufficient anti-tuberculous treatment period underwent SCT without TB reactivation. ATG, a polyclonal immunoglobulin that directly depletes T cells, has been widely used to reduce graft rejection and GVHD. Despite these advantages, some doctors have expressed concerns about increased risk of infection (27) and delayed immune reconstitution (25), which could promote reactivation of TB following SCT. In our study, 7 patients received ATG as a conditioning regimen at a dose from 2.5 mg/kg to 10 mg/kg, and none suffered TB reactivation.

Although we cannot draw concrete conclusions from this study, with a small population and retrospective design, we suggest that at least patients with proven TB should only receive SCT after a minimum of 100 days of anti-tuberculous treatment. Our data reveal that the extent of TB, the intensity of the conditioning regimen, and the use of ATG for conditioning were not associated with reactivation of TB after SCT.

In conclusion, SCT after >100 days of anti-tuberculous medication could be feasible and safe, in terms of TB control, for patients with hematologic diseases, once clinical, microbiologic, or radiologic improvement in TB has been achieved, although future studies are needed to confirm this finding. The numbers in this study are not sufficient to extend the recommendation (of 100 days of pre-SCT therapy) to patients with drug-resistant TB, but the successful transplantation of 1 patient with isoniazid-resistant TB after 215 days of pre-transplant SCT therapy suggests that this, too, may be feasible with longer durations of pre-SCT therapy, although this should be confirmed in larger studies. The whole duration of anti-tuberculous medication was 12 months in most patients, and most of them did not experience treatment failure for their TB. The duration of anti-tuberculous medication remains a controversial area that warrants prospective study with a larger population.

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