Biology of Blood and Marrow Transplantation 6:370-374 (2000)

#99-068-Budak-Alpdogan

The Frequency of Tuberculosis in Adult Allogeneic Stem Cell Transplant Recipients in Turkey

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(Received December 1, 1999; accepted March 13, 2000)

ABSTRACT

In general, tuberculosis (Tb) is rarely seen in allogeneic stem cell transplant (alloSCT) recipients, but this observation has been challenged in developing countries such as Turkey, where Tb infection is more prevalent than in Europe and the US. In this retrospective study, we report on the incidence of Tb infections in 351 alloSCT recipients at 4 bone marrow transplantation units in Turkey over the last 10 years. The frequency of Tb in alloSCT recipients after allografting (5 of 351) was far greater than that in the general population (35.4 per 100,000). Of the 351 patients who underwent alloSCT, 77 who received isoniazid (INH) chemoprophylaxis for 6 months did not develop posttransplantation Tb. However, 5 of the remaining 274 patients who received no chemoprophylaxis developed Tb a median of 12 months (range, 10-47 months) after allografting. Antituberculosis therapy resulted in complete recovery in all cases. In 2 additional patients who were found to have active pulmonary Tb at the time of transplantation, alloSCT was delayed until the infections were treated. Infections of mycobacteria other than *Mycobacterium tuberculosis* were not observed. The number of patients who received and tolerated INH may not be sufficient for firm conclusions, but the data suggest that, in countries where Tb is prevalent, pre- and posttransplantation follow-up for Tb and the use of INH prophylaxis should be considered.

KEY WORDS

Stem cell transplantation • Allogeneic • Tuberculosis • Mycobacteria

INTRODUCTION

The reported frequency of *Mycobacterium tuberculosis* infection in solid organ transplant recipients varies from 0.2% to 15% (mean, 3.7%), which is 6 to 62 times higher than the frequency in the general population (0.01% to 0.045%) [1]. The incidence of tuberculosis (Tb) in the general population is the principle predictor of the increased frequency noted in the transplant recipients. In North America, solid organ recipients experience posttransplantation Tb at a frequency of 0.5% to 1%, whereas recipients from countries in which Tb is more prevalent, such as India and Pakistan, report a frequency of approximately 9% [1]. In comparison with solid organ transplant recipients, allogeneic stem cell transplant (alloSCT) recipients have rarely been reported to develop mycobacterial infections. In Western countries, the frequency of Tb in these patients is lower, varying between 0.13% and 2.2%, probably because of the transfer of purified protein derivative (PPD)-specific T-cell immunity of the donor and the shorter period of immunosuppression compared with that of solid organ transplant recipients [2-8]. However, lower prevalence of Tb infection after alloSCT has not been confirmed in developing countries, such as Turkey, where Tb infection is more prevalent [9].

The aim of this retrospective survey was to determine the frequency of Tb infection in adult alloSCT recipients in Turkey and to evaluate the influence and toxicity of isoniazid (INH) prophylaxis.

PATIENTS AND METHODS

This retrospective survey was carried out at 4 bone marrow transplantation (BMT) units in Turkey. A total of 351 adult alloSCT recipients were studied: 185 patients from Ankara Ibni-Sina Hospital (A), 74 patients from Istanbul School of Medicine (I), 50 patients from Cerrahpasa School of Medicine (C), and 42 patients from Marmara School of Medicine (M) (Table 1). We reviewed the hospital and outpatient follow-up records of these 351 patients who underwent unmanipulated alloSCT between January 1988 and August 1998.

Table 1. *Demographic and Clinical Features of the Patients**

Bone marrow transplantation unit	
Ankara Ibni-Sina Hospital	**185**
Istanbul School of Medicine	**74**
Cerrahpasa School of Medicine	**50**
Marmara School of Medicine	**42**
Female sex	**132 (37.6)**
Age, y (median [range])	**30 (15-54)**
Graft source	
Peripheral blood stem cells	**146 (41.6)**
Bone marrow	**205 (58.4)**
GVHD prophylaxis	**Cyclosporin A and short-term methotrexate**
Primary diagnosis	
Acute myeloblastic leukemia	**135 (38.5)**
Acute lymphoblastic leukemia	**48 (13.7)**
Chronic myeloid leukemia	**114 (32.5)**
Other†	**54 (15.4)**
Conditioning regimens	
Cy/TBI‡	**89 (25.4)**
Bu/Cy ± VP16§	**244 (69.5)**
Other	**18 (5.1)**
Acute GVHD	**172 (49)**
Grade II-IV	**119 (33.9)**
Veno-occlusive disease	**13 (3.7)**

*Data are n or n (%), unless otherwise specified. GVHD indicates graft-versus-host disease.
†Aplastic anemia, multiple myeloma, and myelodysplastic syndrome.
‡Cyclophosphamide (120 mg/kg) and total body irradiation (12 Gy).
§Busulfan (16 mg/kg) and cyclophosphamide (120 mg/kg) with or without etoposide (30 mg/kg).

All transplants were from HLA-matched relatives: 347 were HLA-identical siblings; 2 were HLA-identical nonsibling family members; and 2 were siblings with a single HLA antigen mismatch. The median age was 30 years (range, 15-54 years), 132 (37.6%) of the patients were female, and 219 (62.4%) were male (Table 1). The primary diagnosis was acute myeloblastic leukemia (AML) in 135 patients (38.5%), acute lymphoblastic leukemia in 48 patients (13.7%), and chronic myeloid leukemia (CML) in 114 patients (32.5%); the remaining 54 patients (15.4%) had severe aplastic anemia, myelodysplastic syndrome (MDS), or multiple myeloma (Table 1). All had been vaccinated in infancy with bacillus Calmette-Guérin (BCG).

All patients received the same graft-versus-host disease (GVHD) prophylaxis of cyclosporin A and short-term methotrexate. Diagnosis and grading of acute GVHD were based on clinical evaluation and histologic confirmation [10], and the patients who had grade II to IV acute GVHD were treated. Chronic GVHD and veno-occlusive disease (VOD) were diagnosed and graded according to Seattle criteria [11,12].

The 4 transplant units had different pretransplantation evaluation schedules and posttransplantation prophylaxis policies with respect to Tb. All centers screened patients with chest radiogram before transplantation, and patients who had infiltrates or suspicious lesions were evaluated with computed tomography and, if required, bronchoscopy. Two centers (A and C, accounting for 235 patients) did not give patients the tuberculin skin test before transplantation, nor did they give INH prophylaxis after allografting. In the other 2 BMT units (I and M, accounting for 116 patients), all the recipients were screened by intradermal injection of 5 units of tuberculin PPD (Mantoux test) before alloSCT. All PPD readings were made by pen technique at 72 hours according to Howard and Solomon [13]. The Mantoux test was not repeated in patients with negative results. In BMT unit I, all 74 patients, regardless of Mantoux test results, received INH prophylaxis at a dose of 300 mg/day po starting 5 days before alloSCT and continuing for 6 months. In BMT unit M, only the patients who had a positive tuberculin reaction (an induration greater than 15 mm at 72 hours) (3 of 47 patients) received the INH prophylaxis.

All samples, including sputum, bronchoalveolar lavage fluid, and urine, were evaluated for acid-fast bacilli by direct examination of the sample with Ziehl-Neelsen stain, and all were cultured using either Lowenstein-Jensen medium or BACTEC-460 liquid medium (BD Biosciences, Cedex, France).

Serum aminotransferase (alanine and aspartate transaminase [ALT and AST]) levels were closely followed for signs of hepatotoxicity in patients receiving INH prophylaxis. During the first month, serum aminotransferase levels were checked every other day, and then weekly for 6 months. Aminotransferase elevations of 2- to 3-fold without associated findings of VOD, acute GVHD [11,12], or cyclosporin A toxicity prompted a cessation of INH. If aminotransferase elevations continued despite cessation of INH, the other prophylactic drugs (such as fluconazole, trimethoprim-sulfamethoxazole, and acyclovir) were considered to be the cause of hepatotoxicity, and their gradual elimination was pursued. Also, in the patients who had progressive hepatic deterioration due to either VOD or acute GVHD, INH prophylaxis was halted.

RESULTS

Of the 116 recipients in 2 centers (I and M) who were tested before alloSCT, the PPD reaction size was less than 10 mm in 80 (69%), 11 to 15 mm in 29 (25%), and >15 mm in 7 (6%) (Table 2). None of the 7 patients (3 from center M and 4 from center I) who had a positive PPD with a normal chest radiogram before transplantation developed posttransplantation Tb (Table 2).

Posttransplantation Tb infection occurred in 5 of 351 patients. These 5 patients (3 from center M and 2 from center A) had normal chest radiograms before transplantation. In 2 patients at center A, PPD was not tested before transplantation; interestingly, PPD was <10 mm in the other 3 patients (center M) (Table 3).

Tb diagnosis was "certain" in 4 cases: *M tuberculosis* was cultured from sputum or from bronchoalveolar lavage fluid in 3 patients and from urine in 1 patient. Tuberculosis was considered "probable" in 1 patient who had a clinical picture highly suggestive of Tb: right upper lobe infiltration, night sweats, weight loss, and sustained fever. His pneumonia did not resolve with azithromycin but did resolve with antituberculous treatment. None of the patients with Tb had copathogens. Infections due to mycobacteria other than *M tuberculosis* were not encountered. No patient had a known personal or family history of Tb, and none had a his-

Table 2. *Posttransplantation Tuberculosis in Allogeneic Stem Cell Transplant Recipients by Pretransplantation Tuberculin Test and Isoniazid Prophylaxis**

BMT Center	Pretransplantation PPD Reaction, mm			Isoniazid Prophylaxis	
	<10	11-15	>15	Not Given	Given
Ankara Ibni-Sina Hospital (n = 185)					
Total	ND	ND	ND	185	0
Developed posttransplantation tuberculosis	—	—	—	2	—
Cerrahpasa School of Medicine (n = 50)	ND	ND	ND	50	—
Marmara School of Medicine (n = 42)					
Total	30	9	3	39	3
Developed posttransplantation tuberculosis	3	0	0	3	0
Istanbul School of Medicine (n = 74)	50	20	4	0	74
All centers (n = 351)					
Total	80	29	7	274	77
Developed posttransplantation tuberculosis	3	0	0	5†	0†

*Data are n. PPD indicates purified protein derivative; ND, not done.
†$P = .59$ by Fisher exact test.

tory of close contact with someone who had active Tb. Clinical characteristics of these patients, including results of the tuberculin reaction before transplantation, time of Tb diagnosis, and GVHD stages, are summarized in Table 3.

Two patients had pulmonary Tb at the time of alloSCT. In one, whose primary diagnosis was CML, alloSCT was carried out after a complete 6-month course of antituberculous treatment. The other, who had AML transformed from MDS, received antituberculous drugs for 4 months followed by alloSCT with antituberculous treatment. The disease has not recurred in either of the 2 patients.

In only 1 alloSCT recipient, who had Tb 15 months after transplantation, grade II acute GVHD and extensive chronic GVHD were observed before the development of pulmonary Tb (Table 3). This patient had received prednisolone for the treatment of acute GVHD for a period of 5 weeks beginning on day 45. Nine months after the alloSCT, he was diagnosed with chronic extensive GVHD, the symptoms of which were controlled with readministration of cyclosporin A. His Tb-related symptoms appeared 6 months after the diagnosis of chronic GVHD and 15 months after the alloSCT.

Of the 351 patients, 77 received INH chemoprophylaxis for 6 months. None of these patients developed posttransplantation Tb; 5 of the remaining 274 cases developed Tb (4 pulmonary and 1 renal) 10 to 47 months (median, 13 months) after allografting (Table 3). All 3 patients from center M were given the same antituberculous treatment consisting of INH (300 mg/day) and rifampin (600 mg/day) for 9 months and ethambutol hydrochloride (15 mg/kg per day) and pyrazinamide (2 g/day) for 2 months. Patient 5 (center A) had similar antituberculous treatment but received ethambutol and pyrazinamide for 3 months instead of 2 months. Patient 4 (center A) received INH (300 mg/day) and rifampin (600 mg/day) for 12 months, ethambutol (15 mg/kg per day) for 4 months, and pyrazinamide (2 g/day) for 2 months. In all cases, antituberculous therapy resulted in complete eradication of the infection.

In 77 patients who received INH prophylactically, no drug-related hepatotoxicity (defined as AST more than 5 times normal and development of hepatitis symptoms) was observed. However, intervening hepatic GVHD involvement in 9 patients and VOD in 4 patients necessitated interruption of INH administration during the search for the cause of hepatotoxicity. After evaluation and treatment of liver function deterioration, INH prophylaxis was reestablished in 4 of the 13 patients; the other 9 patients (4 with VOD and 5 with acute GVHD) died of transplant-related disorders.

DISCUSSION

In general, alloSCT recipients have impaired T-cell–mediated cellular immunity as a consequence of the primary

Table 3. *Clinical Characteristics of Allogeneic Stem Cell Transplant Recipients Who Developed Posttransplantation Tuberculosis**

Patient	BMT Unit	Age, y	Sex	Primary Diagnosis	Allograft Source	Pretransplantation PPD Reaction, mm	Time of Diagnosis, mo	Infection Site	aGVHD Grade	cGVHD
1	M	21	M	CML	BM	6	>11	Pulmonary	I	—
2	M	16	F	CML	BM	4	>10	Renal	I	—
3	M	24	M	AML	BM	9	>47	Pulmonary	I	—
4†	A	42	M	AML	PBSCs	ND	>12	Pulmonary	0	—
5†	A	34	M	CML	PBSCs	ND	>15	Pulmonary	II	Extensive

*BMT indicates bone marrow transplantation; PPD, purified protein derivative; aGVHD, acute graft-versus-host disease; cGVHD; chronic graft-versus-host disease; CML, chronic myeloid leukemia; BM, bone marrow; AML, acute myeloblastic leukemia; PBSCs, peripheral blood stem cells; ND; not done.
†Previously reported by Arslan et al. [8].

Table 4. *Mycobacterium Tuberculosis Infections After Allogeneic Stem Cell Transplantation*

Authors	Reference	Country	Year	Frequency	General Incidence (%) [Reference]
Navari et al.	[2]	US	1983	7/682 (1.0%)	0.01-0.03 [16,17]
Kurzrock et al.	[3]	US	1984	2/90 (2.2%)	0.01-0.03 [16,17]
Rouleau et al.	[4]	France	1993	1/420 (0.2%)	0.015-0.033 [18]
Hoyle and Goldman	[5]	UK	1994	3/1007 (0.3%)	<0.01 [19]
Roy and Weisdorf	[6]	US	1995	2/1486 (0.1%)	0.01-0.03 [16,17]
Martino et al.	[7]	Spain	1996	2/118 (1.7%)	0.03-0.045 [20]
Arslan et al.	[8]	Turkey	1998	2/120 (1.7%)	0.0354 [9]

disease itself or as adverse effects of the treatment, and they usually require at least 12 months to recover that immunity [14,15]. Therefore, a higher frequency of Tb infections would be anticipated.

This retrospective survey shows that in adult alloSCT recipients in Turkey, the risk of developing Tb after alloSCT is not negligible. The observed posttransplantion Tb frequency in our group (5 of 351 patients) was far greater than the incidence of Tb in the general population of Turkey (35.4 per 100,000) (Table 4) [9]. However, Tb infections in alloSCT recipients occur less frequently than in solid organ transplant recipients. This disparity may, at least in part, be due to the long duration of immunosuppression in recipients of solid organ transplants and the long-term persistence of transferred PPD-reactive T cells from the stem cell donor [4,6,7].

BCG is a compulsory vaccine for infants in Turkey; as shown by Rouleau et al. [4], vaccination with BCG could provide anti-PPD reactive T-cell clones of donor origin in alloSCT recipients. Therefore, the evaluation of donor tuberculin skin test reactivity before allografting may be valuable.

Despite previous vaccination, 80 of the 116 recipients had a tuberculin reaction <10 mm (ie, PPD-negative) before transplantation. On the other hand, in BMT unit M, 3 recipients who developed posttransplantation Tb (patients 3, 4, and 5) did not receive any prophylaxis because their PPD results were <10 mm (Table 3). These 2 observations raise the question as to whether PPD reactions should be routinely tested in this group of patients and whether only PPD-positive (>15 mm) candidates should receive INH.

In our study, none of the 77 patients under INH prophylaxis developed Tb after alloSCT, and none experienced deleterious INH-induced hepatotoxicity. INH chemoprophylaxis markedly reduces the risk of developing active Tb, especially for recently infected individuals. Fatal INH-related toxicity has been observed much less frequently than had once been suggested [21]. Adherence to World Health Organization guidelines for administration and monitoring of INH prophylaxis has helped reduce its adverse effects [21]. Furthermore, a recent study on renal transplant recipients showed that the risk of developing serious hepatotoxicity after administration of INH was low and similar to that of the normal individual [22]. No comparable INH toxicity data for alloSCT recipients has been published.

According to our observations, Tb seems to be among the late infections following alloSCT, and therefore the timing of INH chemoprophylaxis is also debatable. AlloSCT recipients might start receiving INH prophylaxis 3 to 6 months after allografting, when interference from other drug toxicities, GVHD, or VOD is usually much less than during the first 100 days.

All our patients with Tb, like the patients in the series mentioned in Table 4, recovered successfully with antituberculous treatment. Therefore, treating the documented infection at the time of diagnosis could also be an alternative to chemoprophylaxis. Nevertheless, only randomized trials can determine whether prophylaxis or treatment at diagnosis is a more efficient approach for posttransplantation Tb.

There was no statistically significant difference in the posttransplantation Tb frequency between the groups who did (0 of 77) or did not (5 of 274) receive INH prophylaxis (P = .59). However, the frequency of Tb among alloSCT recipients in Turkey (5 of 351) was found to be far above that in the general population (35.4 per 100,000). These data suggest that the merits of INH prophylaxis among alloSCT recipients should be addressed in a larger, randomized, controlled clinical trial. Especially in countries where Tb is prevalent, there should be meticulous pretransplantation testing and posttransplantation follow-up for Tb. Also, because INH was apparently well tolerated, we recommend that the use of INH chemoprophylaxis should be considered.

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