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Latent tuberculosis in adult hematopoietic stem cell transplantation recipients

Clinical experience from a previously endemic population

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Abstract

Hematopoietic stem cell transplantation (HSCT) recipients may be at an elevated risk of developing active tuberculosis infection due to suppression in the cellular immune system. Herein, we aimed to evaluate the prevalence of latent tuberculosis and active tuberculosis in patients with allogeneic and autologous HSCT. In this cohort, data were obtained retrospectively from patients' records. The patients who were followed up in the bone marrow transplantation unit of the University of Health Sciences Dr Abdurrahman Yurtaslan Ankara Oncology Education and Research Hospital between January 2016 and December 2019 were screened for the study. And the HSCT recipients who had tuberculin skin test and/or QuantiFERON-TB gold (QFT-GIT) test results were included in the study. A total of 361 patients were included in the study, 227 patients had autologous HSCT, and 134 patients had allogeneic HSCT. QFT-GIT was performed in 10 patients with allogeneic HSCT, and it was found positive in only 1 patient. Tuberculin skin test ≥5 mm was accepted as positive and was accepted to have latent tuberculosis, and it was positive in 18.2% (41) of the patients with autologous HSCT and was positive in 21.6% (29) of the patients with allogeneic HSCT. There was no significant difference between the 2 groups (P = .429). Isoniazid (INH) prophylaxis was started in 16.7% of patients with autologous HSCT and 22.4% of patients with allogeneic HSCT. During follow-up, active tuberculosis did not develop in any patients in both groups. There was no statistically significant difference found between allogeneic and autologous HSCT recipients regarding the prevalence of latent tuberculosis. Active tuberculosis infection did not develop in any of the patients who started INH prophylaxis. INH prophylaxis seems to be very efficient in preventing the reactivation of latent tuberculosis in patients going through allogeneic HSCT and/or autologous HSCT.

Abbreviations: HSCT = hematopoietic stem cell transplantation, INH = Isoniazid, QFT-GIT = QuantiFERON-TB gold.

Keywords: allogeneic HSCT, autologous HSCT, INH prophylaxis, tuberculosis

1. Introduction

Patients with hematopoietic stem cell transplant may have a severe impairment in cellular immunity due to immunosuppressive treatments, preparation regimens used for transplantations, infections (such as cytomegalovirus), and/or potentially developed graft-versus-host diseases.[1] Akan et al suggested that prophylactic treatment could only be an option for selected patients or countries with high rates of tuberculosis.[2]

The total number of patients diagnosed with tuberculosis in Turkey in 2017 was 12,046 of which 92.2% were new cases and 7.8% were previously treated cases; women 42.3%, men 57.7%; those with lung involvement were 66.1%, and those with only extrapulmonary organ involvement were 33.9% in Turkey.[3] The incidence of registered tuberculosis in Turkey has decreased by an average of 5% annually for the last 10 years.[3]

In their cohort of 641 adult bone marrow transplant patients, Aljurf et al reported 4 patients developed active tuberculosis.[4] Among them, the onset of infection ranged from 120 days to 20 months post-hematopoietic stem cell transplantation (HSCT).[4] Another large study from India reported 2.3% of the HSCT patients developed tuberculosis.[5] Similarly, Lee et al reported 3.1% of the 295 transplant recipients were diagnosed with Mycobacterial infections.[6] The time

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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from HSCT to tuberculosis infection ranged from 45 days to 165 days posttransplantation.[6] Russo et al reported an allogeneic transplantation case who developed tuberculosis 8 days after his HSCT.[7] Kuan et al reported a post-autologous stem cell transplantation patient who developed progressive pancytopenia and myeloid maturation arrest 2 and a half months after the transplant and was treated well with anti-tuberculosis treatment.[8]

To date, there is still ongoing research on the prevalence of latent tuberculosis information and the practical strategies regarding preventing active tuberculosis in this specific population. In this study, we reported the prevalence of latent tuberculosis and active tuberculosis in patients with allogeneic and autologous HSCT.

2. Material and method

In this retrospective study, we obtained the data from patient records. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local hospitals' ethics committee (Ethics Committee at the University of Health Sciences Dr Abdurrahman Yurtaslan Ankara Oncology Education and Research Hospital). (Date: January 22, 2020 and decision no: 2020-01/517).

The data of the patients who were followed up in the bone marrow transplantation unit of the Ankara Dr Abdurrahman Yurtaslan Oncology Education and Research Hospital between January 01, 2016 and December 31, 2019 was reviewed. The HSCT recipients who had tuberculin skin test and/or QuantiFERON-TB gold (QFT-GIT) were included in the study.

Current diagnoses and other results of the patients were accessed electronically as a retrospective file search. Demographic data and additional information of the patients were recorded on a pre-prepared form. In the form, the patient's name-surname, gender, age at the time of transplantation, underlying hematological malignancy (acute lymphoblastic leukemia, acute myeloid leukemia, Hodgkin lymphoma, chronic lymphoblastic leukemia, chronic myeloid leukemia, myelodysplastic syndrome/myeloproliferative neoplasia, multiple myeloma, non-Hodgkin lymphoma, other), any potential findings suggestive of tuberculosis in pre-transplant on chest x-ray or thoracic tomography, type of transplantation (allogeneic, autologous), positive tuberculin skin test (≥5 mm), QFT-GIT results, information about the initiation of prophylaxis Isoniazid (INH) 100 mg 1 × 3/daily peroral (1 × 300 mg/daily) and any history of the development of active tuberculosis at the end of the follow-up were recorded. The data of patients with allogeneic and autologous HSCT were compared. Latent tuberculosis infection is an ongoing, but clinically disease-free status. Latent tuberculosis infection evaluation is important for tuberculosis prevention approaches.[9] Patients who had tuberculin skin test ≥ 5 mm were accepted to have latent tuberculosis. In addition, QuantiFERON-TB gold test positive patients were also accepted to have latent tuberculosis. Furthermore, the standard clinical approach for INH prophylaxis at the Ankara Dr Abdurrahman Yurtaslan Oncology Education and Research Hospital was to start INH prophylaxis before stem cell transplantation and to continue 9 months of INH prophylaxis after stem cell transplantation. Patients under 18 years old, pregnant patients, and patients without HSCT were excluded from the study.

2.1. Statistical analysis

Statistical data analysis was performed using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0, IBM Corp., Armonk, NY). Descriptive statistics and frequency tables were used to evaluate the data. Categorical variables were compared with the chi-square test with continuity correction. $P < .05$ was considered statistically significant.

3. Results

A total of 361 patients were included in the study, 227 patients underwent autologous HSCT, and 134 patients underwent allogeneic HSCT. In the autologous HSCT group, 33.5% (76) of the patients were female and 66.5% (151) men; in the allogeneic HSCT group, 35.1% (47) of the patients were female and 64.9% (87) male. Thirty-seven point four percent (85) patients with autologous HSCT were aged between 46 and 60 years, and 23.8% (54) patients were older than 60 years. 42.5% (57) patients with allogeneic HSCT were aged 30, and below, 29.9% (40) patients were aged between 31 and 45 years.

The most common diagnosis among autologous HSCT receipts was multiple myeloma (50.7%), followed by non-Hodgkin lymphoma (24.7%). On the other hand, acute myeloid leukemia was the most common diagnosis in patients with allogeneic HSCT (48.5%), followed by acute lymphoblastic leukemia (25.4%) (Table 1).

Tuberculin skin test was positive (≥5 mm) in 18.2% (41) patients with autologous HSCT, and 21.6% (29) patients with allogeneic HSCT were positive. There was no statistically significant difference between the 2 groups ($P = .429$). The rate of findings suggestive of latent tuberculosis on chest X-ray or thorax computed tomography did not differ between autologous HSCT and allogeneic HSCT receipts (3.5% vs 3%, respectively) (Table 1). QFT-GIT test (Cellestis Limited, Carnegie, Australia) was performed in 10 patients with allogeneic HSCT, and it was found positive in only 1 patient. It was performed on 2 patients with autologous HSCT, and it was found to be negative. No significant difference was found between the 2 groups (Table 1). INH prophylaxis was started in 16.7% (38) patients with autologous HSCT and 22.4% (30) patients with allogeneic HSCT. There was no patient whose transplant was delayed due to INH prophylaxis. The last time to control the patients' records for any reactivation history was June 1, 2021. Active tuberculosis infection did not develop after the stem cell transplantation in any of the patients in both groups (Table 1).

4. Discussion

Tuberculosis is a worldwide public health problem that may cause severe opportunistic infections, especially in endemic areas. The risk of tuberculosis infection in HSCT receipts may vary on the underlying disease, including decreased *T* cell count, other co-existing conditions, presence of graft-versus-host diseases, chemotherapy given before transplantation, other immunosuppressive drugs, and use of corticosteroids.[2,6,7,10,11] In this study, there was no statistically significant difference in the prevalence of latent tuberculosis in allogeneic HSCT and autologous HSCT recipients. In both groups, the frequency of patients who started INH prophylaxis was similar, and no significant difference was found. Active tuberculosis infection did not develop in both groups. Budak-Alpdogan et al reported that the incidence of tuberculosis after allografting was 1.42% (5/351), and the patients who received INH chemoprophylaxis did not develop post transplantation tuberculosis.[12] Even though Turkey was an endemic region for tuberculosis infection, none of the allogeneic transplant recipient patients in our study developed tuberculosis reactivation infection. This was attributed to relevant INH prophylaxis.

Currently, there is no consensus on the screening strategies and the utilization of primary prophylaxis for latent tuberculosis. WHO (World Health Organization) had a goal to end the global tuberculosis epidemic.[13] Tuberculin skin test and QFT-GIT could be used in the diagnosis of latent tuberculosis. Blood assays called interferon gamma release assays (IGRAs) contain *M. tuberculosis* antigens that enhance specificity.[14] QFT-GIT and T-SPOT.TB are two known types of IGRAs.[14] On the other hand, Sester et al reported that progression to tuberculosis was not predicted very well by these tests.[15] The effectiveness of

Table 1

Comparison of data between groups.

Variable (N = 361)	Autologous (n = 227)		Allogeneic (n = 134)		Statistical analysis* Possibility
	n	%	n	%	
Gender					
Female	76	33.5	47	35.1	$\chi^2 = 0.095$
Male	151	66.5	87	64.9	$P = .757$
Age groups					
≤30	38	16.7	57	42.5	$\chi^2 = 47.653$
31–45	50	22.1	40	29.9	***P* = .000**
46–60	85	37.4	31	23.1	
>60	54	23.8	6	4.5	
Hematological malignancy					
ALL	2	0.9	34	25.4	$\chi^2 = 245.742$
AML	1	0.3	65	48.5	***P* = .000**
HL	39	17.2	12	9.0	
CML	–	–	2	1.5	
MDS/MPN	–	–	2	1.5	
MM	115	50.7	1	0.7	
NHL	56	24.7	11	8.2	
Diğer	14	6.2	7	5.2	
Findings suggestive of tuberculosis history in pre-transplant chest X-ray or thorax tomography					
Positive	8	3.5	4	3.0	$\chi^2 = 0.000$
Negative	219	96.5	130	97.0	$P = 1.000$
Tuberculin skin test (≥5 mm)					
Positive	41	18.2	29	21.6	$\chi^2 = 0.626$
Negative	184	81.8	105	78.4	$P = .429$
QFT-GIT					
Positive	–	–	1	10.0	$\chi^2 = 0.000$
Negative	2	100.0	9	90.0	$P = 1.000$
INH prophylaxis					
Positive	38	16.7	30	22.4	$\chi^2 = 1.758$
Negative	189	83.3	104	77.6	$P = .185$
Active tuberculosis development at the end of follow-up					
Negative	227	100.0	134	100.0	$P = 1.000$

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, HL = Hodgkin lymphoma, CML = chronic myeloid leukemia, MDS/MPN = myelodysplastic syndrome/myeloproliferative neoplasia, MM = multiple myeloma, NHL = non-Hodgkin lymphoma, GVHD = graft versus host disease, QFT-GIT = QuantiFERON-TB gold, INH = Isoniazid.

*"χ^2" cross tabs were used to examine the relationships of two qualitative variables.

these tests may decrease in patients with an impaired immune system. de Oliveira et al from Brazil reported that the prevalence of latent tuberculosis was 8.7% in HSCT candidates.[16] They did not observe any active tuberculosis in any patients diagnosed with latent tuberculosis before HSCT and received INH prophylaxis. In another study, Akı et al reported that tuberculosis infection did not occur in any recipients under INH prophylaxis.[17] In their study conducted in Iran, Mahmoudi et al found that the prevalence of latent tuberculosis in HSCT recipients was 12%.[18]

On chest X-ray, patients with fibrotic lung lesions suggestive of healed tuberculosis infection and a tuberculin skin test of ≥ 5 mm were considered test positive for the purified protein derivative tuberculin skin test.[19] Moreover, Bacillus Calmette–Guérin vaccine has been used to prevent tuberculosis infection in Turkey. This is a retrospective study, and bias might also be found due to the study's retrospective design. In a study conducted in Mexico, patients before HSCT were evaluated with a tuberculin skin test and thoracic imaging, and latent tuberculosis infection was found in 26.2% of them.[20] Sixty-two point six percent of the patients were evaluated for active tuberculosis infection before HSCT, and no active tuberculosis infection was found.[20] INH prophylaxis was started in 73.3% of those with latent tuberculosis infection, and the frequency of active tuberculosis infection was found to be 0 in 1 year follow-up after transplantation.[20] Active tuberculosis infection was also 0 in our patients. Besides, in our study, the rate of suggestive findings of tuberculosis in pre-transplant chest X-ray or thoracic tomography in patients with HSCT in both groups was relatively low, and no significant differences were found between the groups.

5. Conclusions

Tuberculosis infection is vital in patients with HSCT. Hereby, in this study, there was no difference in the prevalence of latent tuberculosis when allogeneic HSCT and autologous HSCT recipients were compared. Tuberculosis infection did not develop in any of the HSCT recipients of both groups. This has been attributed to the preventive effect of INH prophylaxis. INH prophylaxis seems to be efficient in preventing latent tuberculosis's reactivation in patients going through allogeneic HSCT and/or autologous HSCT.

6. The limitations of the study

The most important limitation of the study was to be retrospective. Therefore, the side effects of INH could not be followed up in the patients. The prospective studies are needed in this area.

Author contributions

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