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 autologous 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.[11] 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
from HSCT to tuberculosis infection ranged from 45 days to 165 days posttransplantation.\textsuperscript{[6]} Russo et al reported an allogeneic transplantation case who developed tuberculosis 8 days after his HSCT.\textsuperscript{[7]} Kuan et al reported a post-autologous stem cell transplantation patient who developed progressive pan-cytopenia and myeloid maturation arrest 2 and a half months after the transplant and was treated well with anti-tuberculosis treatment.\textsuperscript{[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 tuberculosis 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/mayoproliferative 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 tuberculosis skin test (≥ 5 mm), QFT-GIT results, information about the initiation of prophylaxis Isoniazid (INH) 100 mg 1 x 3/daily peroral (1 x 300mg/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.\textsuperscript{[9]} Patients who had tuberculosis 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.
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. [17] 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 $\geq 5$ 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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References

[1] Navari RM, Sullivan KM, Springmeyer SC, et al. Mycobacterial infections in marrow transplant patients. Transplantation. 1983;36:309–13.
[2] Akan H, Arslan O, Akan OA. Tuberculosis in stem cell transplant patients. J Hosp Infect. 2006;62:421–6.
[3] Ministry of Health of the Republic of Turkey, General Directorate of Public Health. Tuberculosis diagnosis and treatment guidelines, Second Edition. Artı6 Media Promotion Printing, Ankara, May 2019. ISBN: 978-975-590-717-8. (Sağlık Bakanlığı Yayın No:1129)
[4] Aljurf M, Gyger M, Alrajhi A, et al. Mycobacterium tuberculosis infection in allogeneic bone marrow transplant patients. Bone Marrow Transplant. 1999;24:551–4.
[5] George B, Mathews V, Srivastava A, et al. Infections among allogeneic bone marrow transplant recipients in India. Bone Marrow Transplant. 2004;33:311–5.
[6] Lee J, Lee MH, Kim WS, et al. Tuberculosis in hematopoietic stem cell transplant recipients in Korea. Int J Hematol. 2004;79:185–8.
[7] Russo RL, Dulley FL, Suganuma L, et al. Tuberculosis in hematopoietic stem cell transplant patients: case report and review of the literature. Int J Infect Dis. 2010;14(Suppl 3):e187–91.
[8] Kuan FC, Lin PY, Hwang CE, et al. Pancytopenia and myeloid maturation arrest in an autologous stem cell transplant recipient. Bone Marrow Transplant. 2011;46:610–1.
[9] Özçelik HU. Treatment in latent tuberculosis infection. Türkiye Klinikleri J Pediatr Sci. 2016;12:70–3.
[10] Cordonnier C, Martino R, Trabasso P, et al. Mycobacterial Infection: a difficult and late diagnosis in stem cell transplant recipients. Clin Infect Dis. 2004;38:1229–36.
[11] Fan WC, Liu CJ, Hong YC, et al. Long-term risk of tuberculosis in hematopoietic stem cell transplant recipients: a 10-year nationwide study. Int J Tuberc Lung Dis. 2015;19:58–64.
[12] Budak-Alpdogan T, Tangın Y, Kalyagolu-Bessik S, et al. The frequency of tuberculosis in adult allogeneic stem cell transplant recipients in Turkey. Biol Blood Marrow Transplant. 2000;6:370–4.
[13] World Health Organization. The end TB Strategy. Available at: https://www.who.int/publications/i/item/WHO-HTM-TB-2015.19. WHO Reference Number: WHO/HTM/TB/2015.19.
[14] Venkatappa TK, Punnoose R, Katz DJ, et al. Comparing QuantiFERON-TB gold plus with other tests to diagnose mycobacterium tuberculosis infection. J Clin Microbiol. 2019;57:e00985–19.
[15] Sester M, van Leth F, Bruchfeld J, et al. Risk assessment of tuberculosis in immunocompromised patients. A TBNET study. Am J Respir Crit Care Med. 2014;190:1168–76.
[16] de Oliveira Rodrigues M, de Almeida Testa LH, Dos Santos AC, et al. Latent and active tuberculosis infection in allogeneic hematopoietic stem cell transplant recipients: a prospective cohort study. Bone Marrow Transplant. 2021;56:2241–7.
[17] Akşı SZ, Sucak GT, Tunçan OG, et al. The incidence of tuberculosis infection in hematopoietic stem cell transplantation recipients: a retrospective cohort study from a center in Turkey. Transpl Infect Dis. 2018;20:e12912.
[18] Mahmoudi S, Pourakbari B, Sadeghi RH, et al. High prevalence of latent tuberculosis in hematopoietic stem cell transplant recipients: a first report. Pediatr Transplant. 2020;24:e13770.
[19] Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America (IDSA), September 1999, and the sections of this statement. Am J Respir Crit Care Med. 2000;161(4 Pt 2):E187–91.
[20] Bourlon C, Camacho-Hernández R, Fierro-Angulo OM, et al. Latent tuberculosis in hematopoietic stem cell transplantation: diagnostic and therapeutic strategies to prevent disease activation in an endemic population. Biol Blood Marrow Transplant. 2020;26:1350–4.