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Original Article

Management of Latent Tuberculosis Infection Based on T-SPOT.TB Assay in Patients with Hematological Malignancies

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Abstract. ***Background and objective:*** **Patients with latent tuberculosis infection (LTBI) receiving chemotherapy for hematological malignancy (HM) are at high risk of developing active tuberculosis (TB) infection. The aim of this study is to show real-life data and results of the T-SPOT test and preventive isoniazid (INH) therapy in pre-chemotherapy LTBI screening in the HM patient group.**
Methods: **This retrospective study includes 209 HM patients who had T-SPOT test between 2016 and 2021 in Sultan 2. Abdulhamid Han Training and Research Hospital in Istanbul, Turkey.**
Results: **The prevalence of LTBI was 26.8% in 209 patients (n=56). Preventive INH therapy was initiated in 82.1% (n=46) of 56 patients with LTBI. 23.9% (n=11) of the 46 patients who received preventive INH therapy were unable to complete the treatment. Nine patients died due to malignancy; one was lost to follow-up, and only one had to stop INH treatment due to elevated liver enzymes. Elevated liver enzymes occurred in 4 (8.7%) patients using INH, while gastrointestinal symptoms occurred in 3 (6.5%) patients. Active TB infection emerged in none of the T-SPOT positive or indeterminate individuals but in one HIV(+) patient in the T-SPOT negative group. The active TB infection incidence rate was 217 cases/100.000hab/year (95% CI, 29-748).**
Conclusions: **INH treatment was generally well tolerated, and very few serious drug-related side effects were observed. Although LTBI cannot be demonstrated in patients with HIV(+) HM who are scheduled for chemotherapy, these patients should be closely monitored for the development of active TB infection.**

Keywords: Hematologic malignancies; Interferon-Gamma Release Assays; Latent tuberculosis.

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Introduction. Turkey has a low incidence of tuberculosis (TB) infection in terms of active TB infection, with a reported incidence of 14.1/100.000 in the general population in 2018.[1] Latent tuberculosis infection (LTBI) is a state of cellular immune response to mycobacterial antigens.[2] The immunosuppression caused by the hematological malignancy (HM) and the agents used in the treatment may lead to TB reactivation.

Thus, patients with LTBI who are receiving chemotherapy for HM are more likely to develop active TB infection.[3] However, there is no worldwide consensus on whether LTBI screening should be performed before chemotherapy in patients with malignancies other than allogeneic hematopoietic stem cell transplantation (HCT) recipients.

Two tests have been developed based on the detection of interferon-gamma (IFN-G) released from lymphocytes against specific antigens of *M. tuberculosis*. These tests, known as The Interferon-Gamma Release Assays (IGRAs), are the Quantiferon®-TB Gold Plus (QFT) and SPOT®.TB (T-SPOT) tests. Compared to the TST, IGRAs yield results with at least comparable sensitivity and better specificity for diagnosing LTBI.[4]

The aim of this study is to retrospectively evaluate the efficacy and safety of the T-SPOT test as well as the preventive INH therapy administered. Thus, the HM patient group aims to share real-life data and results on the administration of preventive INH therapy based on T-SPOT alone in screening for LTBI before chemotherapy.

Material and Methods.

Patients and study design. This retrospective study included 209 patients over 18 diagnosed with HM and having a T-SPOT test for LTBI screening between January 1, 2016, and December 31, 2021, in Sultan 2. Abdulhamid Han Training and Research Hospital in Istanbul, Turkey. This hospital is a tertiary public hospital and a hematology reference center. The T-SPOT test is not performed in our hospital. Instead, patients have the T-SPOT test performed in private laboratories by paying a fee. Those with active TB infection at the time of diagnosis of malignancy, those who did not have a T-SPOT test, those who had TB infection in the past, and those whose health records could not be accessed were excluded from the study. This study was approved by the Ethics Committee of Istanbul Medeniyet University (Decision No: 2022/0027). Due to the study's retrospective nature, written informed consent forms were not obtained from the patients.

Data collection. Age, gender, previous TB history, presence of viral hepatitis and human immunodeficiency virus (HIV), HM type, whether chemotherapy was administered, whether HCT was performed, the type of HCT performed (autologous/allogeneic), comorbid diseases, whether preventive INH therapy was administered, mortality status and follow-up times were recorded. All patients were followed up monthly in the first two months for drug toxicity that may develop due to INH treatment and then for the treatment with laboratory and clinical controls every two months. During follow-up, elevated liver enzymes due to INH were defined as transaminases five-fold higher than the upper limit of normal (ULN) or three-fold higher in the presence of symptoms. In this case, INH treatment was discontinued. In patients who developed transaminase elevations that did not reach critical levels, INH treatment was not discontinued, and these patients were closely monitored. In patients with severe transaminase elevation due to HM involvement of the liver, transaminase levels were expected to decrease with chemotherapy to start INH at the time of diagnosis. If the patient's liver enzymes were more than 3-fold higher than the ULN, INH therapy was initiated when they were < 3-fold the ULN after chemotherapy.

T-SPOT test analysis. T-SPOT.TB® (Oxford, Immunotec, UK) kit was used for T-SPOT test analysis. The test was performed with 5 cc blood samples placed in tubes containing lithium heparin. When the sample was processed in the laboratory, it was placed in a sterile plastic container, 150 µl of T-Cell Xtend (Oxford Immunotec International) was added, and after waiting for a while at room temperature, mononuclear cells were extracted from the serum using a series of centrifugation processes. The collected suspension was transferred to an antigen-coated 4-well plate. In these wells, positive and negative controls, Panel A and Panel B, were analyzed. The prepared plate was incubated for 16-20 hours in a 5% CO2 oven at 37°C. The spots were examined after incubation, numerous pieces of washings, the addition of conjugate, and substrate. T-SPOT.TB positive was considered as eight or more spots, negativity as ≤ 4 spots, and values in the between as borderline.

Patients were divided into three groups: positive, borderline, and negative, according to T-SPOT test results. T-SPOT-positive patients were evaluated by the pulmonology clinic for active TB infection. The patients' lung imaging (lung radiography or lung computed tomography (CT)) and respiratory symptoms (cough, hemoptysis, fever, and/or chills) were thoroughly evaluated. Preventive INH therapy was not administered to T-SPOT test-positive patients who did not receive chemotherapy, underwent low-intensity chemotherapy, declined INH treatment, and had negative or borderline T-SPOT test results. Since there is no clear consensus on indicating LTBI treatment in patients with HM, as a general approach in our clinic, we did not give preventive INH to patients who received low-intensity chemotherapy and did not receive chemotherapy.

Statistical analysis. The prevalence of LTBI was determined by dividing the number of patients with a positive T-SPOT test by the total number of patients. Active TB cumulative incidence was determined by dividing the number of newly diagnosed active TB cases by the total number of patients during follow-up. The person-year method was used to calculate the incidence

rate, and the Poisson regression model was used to calculate the confidence interval (CI). Parametric tests were used without performing the normality test due to the compatibility of the Central Limit Theorem. In the data analysis, the mean and standard deviation of the continuous variables and the minimum and maximum values of the features were used to define the categorical variables, including the frequency and percentage values. One Way ANOVA test statistic was used to compare the mean of three independent groups. Tukey statistic was evaluated as a Post Hoc test if a difference was detected with ANOVA. Chi-square test statistics were used to evaluate the relationship between two categorical variables. Statistical analysis between groups was made according to their T-SPOT results. Median follow-up time is given as median (Q1-Q3) and min-max. In the data evaluation, www.e-picos.com,NY, New York software, and MedCalc Statistical Software version 16.4.3 statistical package software were used.

Results. The study included two hundred-nine patients with HM (**Figure 1**). The clinical and sociodemographic characteristics of the 209 patients participating in the study are shown in **Table 1**. The mean age was 58 (18-85), with a female/male distribution of 81/128.

T-SPOT test results were positive in 56 of 209 patients (26.8%), borderline in 4 (1.9%), and negative in 149 (71.3%). The mean age of those with positive, borderline, and negative T-SPOT tests was 62.1±11.6, 50.8±8.3, and 53.7±17.7, respectively. The mean age of T-SPOT-positive patients was higher than that of negative patients (p=0.001).

Sixty-nine patients (33%) were diagnosed with non-Hodgkin lymphoma, 47 (22.5%) patients with acute myeloid leukemia, 26 (12.4%) patients with multiple myeloma, 22 (10.5%) patients with Hodgkin lymphoma, 22 (10.5%) patients with chronic lymphocytic leukemia, 14 (6.7%) patients with acute lymphoblastic leukemia, 5 (2.4%) patients with myelodysplastic syndrome-myeloproliferative neoplasia (MDS/MPN) and 4 (1.9%) patients with other HM.

The median follow-up period was 740 days (range 2-2119) for the entire population, 732 days (2-2119) for

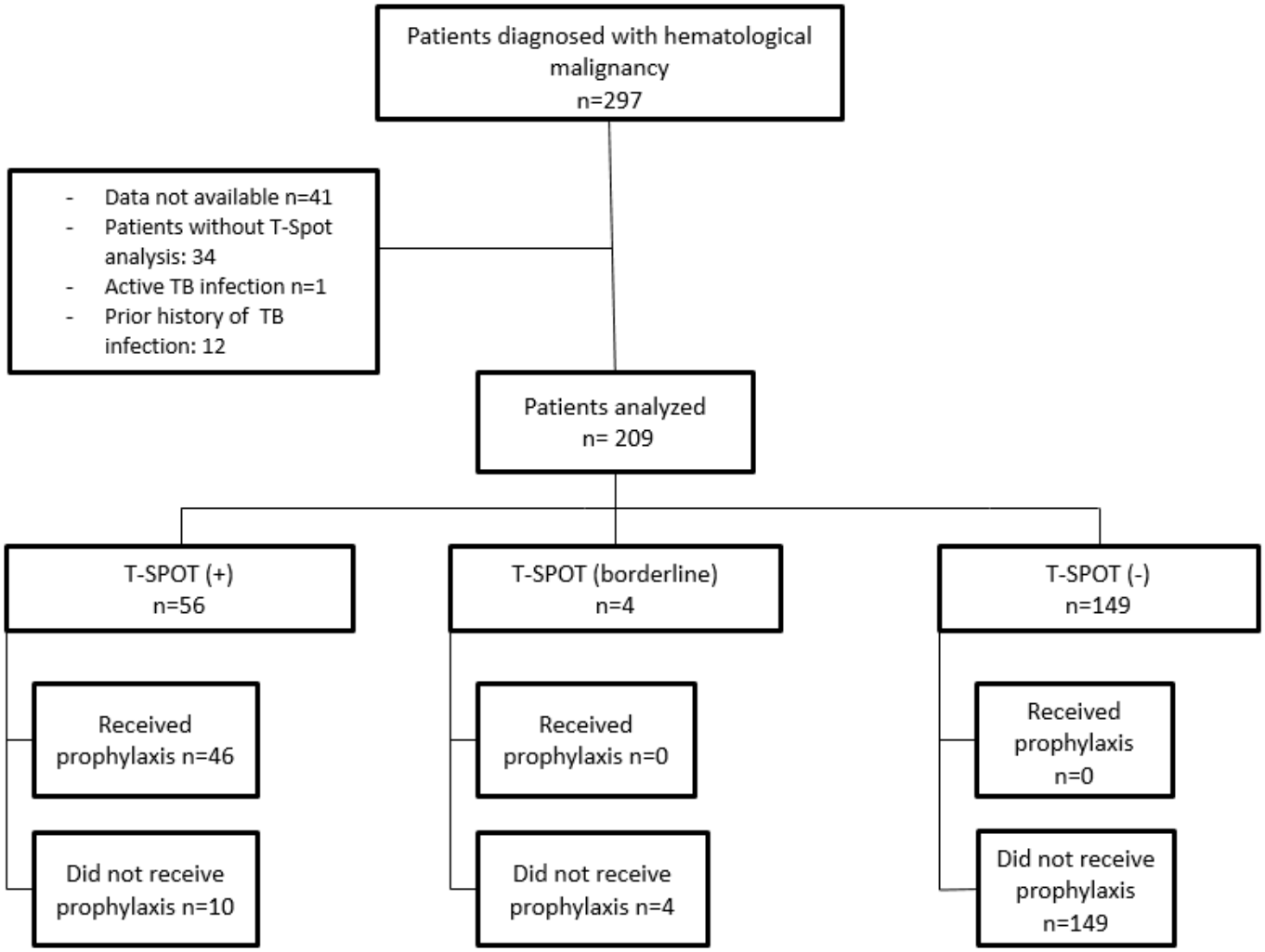

Figure 1. Flowchart of patients with hematological neoplasm. 297 patients with HM were evaluated. Patients whose data could not be obtained (n=41), T-SPOT test could not be performed at the time of diagnosis of HM (n=34), patients with prior TB infection (n=12), and patients diagnosed with active TB infection concurrently with HM diagnosis (n=1) were excluded from the study. 209 patients with HM who had a T-SPOT test for LTBI were included.

Table 1. Clinical and Sociodemographic Characteristics by T-SPOT groups.

Characteristics	Total n=209	T-SPOT Positive n=56 (26.8%)	T-SPOT Borderline n=4 (1.9%)	T-SPOT Negative n=149 (71.3%)
Age, x̄±SD	55.9 ± 16.5	62.1 ± 11.6	50.8 ± 8.3	53.7 ± 17.7
	n (%)	**n (%)**	**n (%)**	**n (%)**
Sex				
Male	128 (61.2)	41 (73.2)	2 (50)	85 (57)
Female	81 (38.8)	15 (26.8)	2 (50)	64 (43)
Viral Serology				
HbsAg +	9 (4.3)	4 (7.1)	-	5 (3.4)
HCV +	1 (0.5)	1 (1.8)	-	-
HIV +	6 (2.9)	-	1 (25)	5 (3.4)
Diagnosis				
AML	47 (22.5)	11 (19.6)	-	36 (24.2)
ALL	14 (6.7)	2 (3.6)	1 (25)	11 (7.4)
NHL	69 (33)	22 (39.3)	2 (50)	45 (30.2)
HL	22 (10.5)	1 (1.8)	-	21 (14.1)
MM	26 (12.4)	11 (19.6)	1 (25)	14 (9.4)
CLL	22 (10.5)	7 (12.5)	-	15 (10.1)
MDS-MPN	5 (2.4)	1 (1.8)	-	4 (2.7)
Others	4 (1.9)	1 (1.8)	-	3 (2)
Chemotherapy				
Not Received	15 (7.2)	4 (7.1)	-	11 (7.4)
Received	194 (92.8)	52 (92.9)	4 (100)	138 (92.6)
Underwent BMT	43 (20.6)	12 (21.4)	2 (50)	29 (19.5)
Bone Marrow Type				
Autologous	21 (48.8)	9 (75)	1 (50)	11 (37.9)
Allogeneic	22 (51.2)	3 (25)	1 (50)	18 (62.1)
Developing Active TB	1 (0.5)	-	-	1 (0.7)
Mortality				
Survivor	117 (56)	30 (53.6)	2 (50)	85 (57)
Exitus	92 (44)	26 (46.4)	2 (50)	65 (43)
Comorbid Disease	102 (48.8)	37 (66.1)	1 (25)	64 (43)
CAD	25 (12)	11 (19.6)	-	14 (9.4)
DM	21 (10)	6 (10.7)	-	15 (10.1)
Cirrhosis	3 (1.4)	3 (5.4)	-	-
CRF	16 (7.7)	4 (7.1)	-	12 (8.1)
HIV	6 (2.9)	-	1 (25)	5 (3.4)
Solid Tumor	5 (2.4)	1 (1.8)	-	4 (2.7)
INH therapy				
Received	46 (22)	46 (82.1)	-	-
Not Received	163 (78)	10 (17.9)	4 (100)	149 (100)

Abbreviations: T-SPOT, SPOT®.TB; **HCV**, hepatitis C virus; **HBsAg**, hepatitis B surface antigen; **HIV**, human immunodeficiency virus; **AML**, acute myeloid leukemia; **ALL**, acute lymphoblastic leukemia; **NHL**, non-hodgkin lymphoma; **HL**, hodgkin lymphoma; **MM**, multiple myeloma; **CLL**, chronic lymphocytic leukemia; **MDS-MPN**, myelodysplastic syndrome-myeloproliferative neoplasia; **BMT**, bone marrow transplantation; **TB**, tuberculosis; **DM**, diabetes mellitus; **CRF**, chronic renal failure; **INH**, isoniazid; **CAD**, coronary artery disease.

those with negative T-SPOT test, 808 days (10-2093) for those with positive T-SPOT test, 523 days (99-680) for those with borderline T-SPOT test, and 785 days (26-2093) for 46 patients with positive T-SPOT test and whose INH was started. During this period, 94 (45%) of 209 patients died due to malignancy. It was found that 26 (46.4%) patients with positive T-SPOT test were dead. No death from TB infection or toxic effect of INH

therapy was observed. While 194 (92.8%) of 209 patients received chemotherapy, chemotherapy was not administered to 15 (7.2%) patients. 4 (7.1%) of 56 patients with positive T-SPOT test did not receive chemotherapy. HCT was performed in 43 (20.6%) of 209 patients, of which 21 (48.8%) autologous HCT and 22 (52.2%) allogeneic HCT were performed. Comorbidities were found in 102 (48.8%) of the patients. Most frequently, coronary artery disease was found in 25 patients (12.2%), followed by diabetes mellitus in 21 (10%) patients, chronic renal failure in 16 (7.7%) patients, viral hepatitis in 10 (4.8%) patients, HIV positivity in 6 (2.9%) patients, solid tumor in 5 (2.4%) patients.

The prevalence of LTBI was 26.8% in the patients included in the study. Preventive INH therapy was initiated in 46 (82.1%) of 56 patients with LTBI, while preventive INH therapy was not initiated in 10 patients. Two (20%) of these patients did not receive preventive INH therapy because they did not accept prophylactic treatment, 4 (40%) were followed without chemotherapy, and 4 (40%) received low-intensity chemotherapy. The patients were scheduled to receive preventive INH therapy at a 300 mg/day dose for nine months. Only 1 out of 46 patients had to stop their INH treatment due to adverse effects. However, 1 (2.2%) patient was lost to follow-up, and 9 (19.6%) patients died due to malignancy before the preventive therapy period was completed.

The patients were followed up for side effects related to INH. Elevated liver enzymes developed in 4 (8.7%) patients, and gastrointestinal symptoms developed in 3 (6.5%) patients. Except for one patient whose preventive INH therapy was discontinued due to liver enzymes five-fold higher than the ULN without any symptom, no indication for interruption or complete discontinuation of treatment occurred in the other patients.

Three of the 209 HM patients had liver enzymes more than 3-fold higher than the ULN at the onset of the disease and before INH, which was started after chemotherapy when the transaminase values of the three patients were less than 3-fold the ULN. After INH treatment, no enzyme elevation was observed in these patients.

Only one of the 209 HM patients developed an active TB infection during the follow-up period. The cumulative incidence of active TB infection was 0.48%, yielding an incidence rate of 217 cases/100.000hab/year (95% CI, 29-748). None of the T-SPOT-positive patients developed active TB infection. Interestingly, the patient who developed active TB infection was found in the T-SPOT-negative group. This patient received R-CODOX-M & R-IVAC (rituximab, doxorubicin, vincristine, cyclophosphamide, cytarabine, methotrexate & rituximab, cytarabine, etoposide, ifosfamide, methotrexate) chemotherapy protocol for a total of 4 months with the diagnosis of plasmablastic lymphoma and HIV(+). The patient's CD4 count was 110 cells/mm^3. Persistent fever, weight loss, and sweating developed approximately one month after chemotherapy was finished and five months after the T-SPOT test. PET/CT revealed pulmonary nodular lesions and intra-abdominal lymphadenomegaly with FDG uptake. In addition, granulomatous inflammation with caseification necrosis was observed in the tru-cut biopsy performed from the lung and intra-abdominal lymph nodes, and acid-fast stained bacilli were observed in the biopsy tissue.

Discussion. The prevalence of LTBI at the time of diagnosis in HM patients was found to be 26.8% in our study. To the best of our knowledge, this study is the first in our country to screen for LTBI using only the T-SPOT test in patients with HM. In our country, different results were encountered when examining the frequencies of LTBI with T-SPOT in non-HM patients. T-SPOT was found positive in 28 (20%) of 141 patients with a mean age of 33, who were sent to them from different branches for a T-SPOT test in a university hospital microbiology laboratory.[5] Binay et al.[6] found a T-SPOT positive rate of 22% in their study of 100 HIV-infected patients. In a study by Senturk et al.,[7] the prevalence of LTBI was 13.8% due to the T-SPOT test performed before anti-TNF treatment in 109 patients with rheumatic disease.

Immunocompromised patients have been shown to have a nine-fold higher risk of developing active TB infection from LTBI compared to the general population.[8] Ganzel et al.[9] found that the MDS/MPN (148.8/100.000 patients) and lymphoma (154.1/100.000 patients) groups had the highest cumulative incidence of active TB infection after a cancer diagnosis. Niu et al.[10] found that 66 of 4712 HM patients developed active TB infection with a prevalence of 1.40%. The prevalence of active TB in HM patients was higher compared to the general population. In our study, the cumulative incidence of active TB in HM patients was found to be 0.48%, with a population rate of 478/100.000. The cumulative incidence of active TB in our HM patient group was substantially higher than in the general population of our country. Thus, all HM patients were considered to be at high risk of developing TB infection.

INH is the most studied and proven medicine in the treatment of LTBI. LTBI treatment with INH for nine months provides 90% protection and appears to be the optimal duration.[11] Elevated liver enzymes caused by INH therapy have been determined in various ways in the literature. Osorio-López et al.[12] planned INH as LTBI treatment for 93 patients with HM for nine months, and they observed 15.1% of drug-related adverse effects. 4.3% of the patients had to discontinue the treatment due to side effects related to INH, and 3.2% (n=3) of them were due to elevated liver enzymes. Sánchez-García et al.[13] observed elevated liver enzymes in 18 (85%) of 21

HM patients due to INH therapy. INH treatment was discontinued in 3 (14%) patients. They mentioned that the higher liver enzymes detected more than the literature could be due to the patients' high mean age. Our study observed side effects related to IHN in 7 (15.2%) patients. INH treatment had to be discontinued in only one patient (2.2%) out of 46 patients due to elevated liver enzymes. Of the 46 patients planned for INH treatment, 35 completed their treatment for nine months. The main reason for not completing preventive INH therapy was early mortality due to malignancy. The lower liver enzyme elevation in our study could be the attention we paid to drug interactions in the selection of chemotherapy in patients scheduled for INH therapy.

T-SPOT test results were borderline in 4 patients (1.9%) in our study population. This rate is roughly comparable to the rates reported in the literature. For example, Rego et al.[14] reported a borderline result rate of 1.8% in 645.947 T-SPOT tests. In our study, these patients were not administered preventive INH therapy, and none developed active TB infection.

The risk of reactivation is greatest within the first two years of Mycobacterium tuberculosis exposure and also reflects LTBI reactivation.[15] The median follow-up period for 46 T-SPOT-positive patients who started INH was more than two years (median 785 (26-2093) days). None of these patients developed active TB infection during the follow-up period. One hundred forty-nine patients who were T-SPOT negative and did not receive preventive INH therapy were followed for a median of 732 days. Only one of these patients developed an active TB infection. The patient who developed active TB infection was diagnosed with active TB infection approximately two months after the chemotherapy ended. The sensitivity of the T-SPOT test in diagnosing LTBI is higher compared to QFT and TST (approximately 90, 80, and 80 percent, respectively).[16] Shangguan et al.[17] investigated risk factors for false-negative T-SPOT results in 833 patients with active TB infection. They found that advanced age, female gender, and HIV coinfection were independent risk factors associated with false-negative T-SPOT.TB results. The sensitivity of the T-SPOT.TB test was found to be 33.3% in HIV-infected active TB patients, and they showed that HIV-positive patients had a 6-fold higher risk of false-negative T-SPOT results compared to negatives. Active TB infection is an opportunistic infection in HIV(+) patients. The risk of developing active TB infection in HIV-infected people is 20-37 times higher than in non-HIV-infected people.[18] Preventive therapy is recommended in these patients in the presence of LTBI. Co-administration of HM and chemotherapy in HIV(+) patients without LTBI, it is thought that it would be prudent to monitor these patients for active TB closely.

Fever, lymphadenomegaly, cough, sweating, loss of appetite, weight loss, and malaise are the most prominent symptoms of active TB infection.[19] Since the symptoms of the two diseases may overlap, the diagnosis of active TB infection may be missed or delayed. Immunosuppression by HM and chemotherapeutic agents may alleviate the symptoms of TB. As a result, a delayed or missed active TB infection has negative effects on mortality in this high-risk population for active TB infection.[20] Silva et al.[21] observed the development of active TB infection at a rate of 2.6% in HM patients during their follow-up, and they found the TB-related mortality rate to be 62.5% in these patients. Our study observed no death from TB infection in 209 patients diagnosed with HM. Therefore, performed LTBI screening and administered preventive INH therapy are considered beneficial.

The mean age of those with positive T-SPOT was significantly higher than those with negative results. The higher rate of LTBI observed in the older age group may be due to increased cumulative exposure to TB bacillus.[22]

Our study had some limitations. First, it was performed retrospectively in a single-center tertiary hospital. Second, we did not include the epidemiologic factors for TB infection in this study, such as occupation (diary workers), socioeconomic status, history of TB exposure, consumption of unpasteurized milk products, and cattle exposure. All these variables might affect the T-SPOT results and also allow the classification of the patients according to their risk, and this could eventually help to identify patients at higher risk of LTBI even with a negative T-SPOT. Third, as this study was conducted in a country with a low TB burden, its results may not apply to countries with moderate-to-high ones.

Conclusions. Although LTBI is difficult to demonstrate in patients living with HIV and HM who are scheduled for chemotherapy, these patients should be closely monitored for the development of active TB infection. INH treatment was generally well tolerated. Serious drug-related side effects were observed very little. There was no interaction with the chemotherapeutics used. Due to advances in cancer treatment, patients with HM have a longer life expectancy in an immunocompromised state, which increases the susceptibility to TB. Thus, it is thought that the risk of TB infection will remain on the agenda in patients with HM.

Authorship Statement. All authors meet the ICMJE authorship criteria. Emrah Kilicaslan and Kadir Canoglu contributed to the study concept and design, as well as data acquisition, interpretation and analysis, writing and critical revision of the final manuscript.

Ethics Committee Approval. This study was approved by the Ethics Committee of Istanbul Medeniyet University Hospital (decision no: 2022/0027).

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