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BRIEF REPORT

Risk of Latent Tuberculosis Reactivation After Hematopoietic cell Transplantation

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There were no cases of tuberculosis in a cohort of 2531 patients who underwent hematopoietic cell transplantation from 2010 to 2015 after 7323 person-years of follow up (95% confidence interval [CI], 0.0–0.05 cases/100 person-years), including 29 (1.15%) patients with untreated latent tuberculosis after 89 person-years of follow-up (95% CI, 0.0–4.06 cases/100 person-years).

Keywords. *Mycobacterium tuberculosis*; TB; LTBI; allogeneic; hematopoietic cell transplantation.

The identification and treatment of individuals with latent tuberculosis infection (LTBI) is crucial to preventing clinical disease [1]. Higher-risk features for LTBI reactivation include malnutrition, human immunodeficiency virus infection, diabetes mellitus, silicosis, end-stage renal disease, recent tuberculosis infection, treatment with glucocorticoids or biological agents, solid organ transplantation, and certain malignancies [2, 3]. Current North American guidelines recommend that individuals at higher risk of tuberculosis reactivation receive preventive therapy [1, 3].

The risk of developing active tuberculosis in persons with a hematological malignancy is increased compared to the general population [4]. However, the magnitude and timing of this risk has not been determined among adult hematopoietic cell transplant (HCT) recipients in low endemic settings. These patients are profoundly immunosuppressed in the peri-transplant period and allogeneic HCT recipients remain therapeutically immunosuppressed for months to prevent and treat graft-versus-host disease (GVHD).

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Although rifampin may be preferred to treat LTBI in certain instances [5], isoniazid has been commonly used to prevent LTBI reactivation after HCT, as it is not associated with significant drug-drug interactions. Patients may be at greatest risk for tuberculosis reactivation early post-transplant, yet starting LTBI therapy at this time is challenging because isoniazid is associated with hepatotoxicity and HCT patients may develop liver injury due to conditioning chemotherapy and other complications. We sought to determine LTBI therapy prescription practices and tuberculosis rates among HCT recipients at our center.

METHODS

We performed a retrospective cohort study involving all adult patients who underwent HCT at the Dana-Farber Cancer Institute/Brigham and Women's Cancer Center between 1 January 2010 and 1 January 2015. Data were censored on 1 April 2018 for the development of tuberculosis. The study was approved by the institutional review board of the Dana-Farber/Harvard Cancer Center Office for Human Research Studies. Patient characteristics and laboratory parameters were collected. Covariates of interest included patient age, sex, country of birth, comorbidities, HCT date, conditioning regimen, HCT source, human leukocyte antigen matching, GVHD prophylaxis regimens, and occurrence of GVHD.

Standard operating procedures at our center mandate that all potential allogeneic HCT recipients undergo LTBI evaluation. Pretransplant tuberculosis screening was generally performed using a 1-step tuberculin skin test (TST) with purified protein derivative without the use of a control antigen [1, 3]. However, 1 of 2 interferon-gamma release assays (IGRA), the QuantiFERON-TB Gold or T-SPOT.*TB*, could be ordered at the physician's discretion when patients could have a false-positive TST due to previous BCG vaccination or for reasons of convenience. The QuantiFERON-TB Gold was used during the first 2 years of the study before the T-SPOT.*TB* was adopted. Per institutional standard operating procedures, patients with LTBI should begin treatment with isoniazid upon discharge from hospital or by day 28 after HCT, whichever occurs first. The infectious diseases service was consulted in cases where isoniazid could not be administered.

To assess LTBI prescription practices, data regarding antimycobacterial therapy were extracted from patient charts. All cases with a positive LTBI screening test identified in the study were independently reviewed by 2 infectious diseases physicians (M. P. C. and T. D. B.) to assess the need for LTBI therapy [1, 3]. Chest imaging, history of Bacillus Calmette–Guérin (BCG)

vaccination, LTBI screening tests, and previous LTBI therapy were reviewed. To assess whether patients developed active tuberculosis, microbiological and pathological data, including autopsy records, were also reviewed. Statistical analyses were conducted using SAS® 9.4 (Cary, North Carolina).

RESULTS

In total, 2531 patients underwent HCT during the study period: 1252 underwent autologous HCT and 1279 underwent allogeneic HCT, 65 of whom had a previous autologous HCT. All patients were screened for latent tuberculosis prior to HCT. Twenty-six patients had both a TST and IGRA, 2 only had an IGRA, and all other patients were screened using a TST. Among the entire cohort, 91 (3.6%) had positive LTBI screening tests prior to HCT, of which 48 (52.7%) were foreign-born. Patient characteristics are presented in Table 1.

Among the 91 patients with positive screening tests, 48 (52.7%) were known to be positive before their pre-HCT evaluation. Of these, 24 had been previously treated, 20 were planned for treatment post-HCT, and 4 patients were not considered to have LTBI given previous BCG vaccination and negative IGRA results. The remaining 43 patients with positive LTBI screening tests were identified as part of their pre-HCT evaluation. Of these, 35 patients had a positive TST, 6 had a positive TST and IGRA, and 2 patients were diagnosed only with a positive IGRA. One patient had an indeterminate IGRA result but was diagnosed with LTBI on the basis of a positive TST result and immigration from a tuberculosis-endemic country. In total, 63 patients diagnosed with LTBI were identified for preventive therapy post-HCT (Figure 1), without disagreements between reviewers. No patient had chest imaging prior to HCT with findings associated with increased risk of LTBI reactivation.

Table 1. Patient Characteristics

	LTBI (n = 91)		Non-LTBI (n = 2440)	
Patient Characteristics	N	(%)	N	(%)
Median age, years (range)	55	19–74	57	18–77
Male sex	53	58.2	1424	58.4
Race				
White	53	58.2	2237	91.7
Black	6	6.6	49	2.0
Asian	11	12.1	34	1.3
Mixed	5	5.5	32	1.3
Unknown	16	17.6	88	3.6
Underlying malignancy for auto-HCT	N = 47		N = 1205	
Multiple myeloma	35	74.5	717	59.5
Non-Hodgkin lymphoma	10	21.3	360	29.9
Hodgkin's disease	2	4.3	106	8.8
Underlying malignancy for allo-HCT	N = 44		N = 1235	
Acute myelogenous leukemia	17	38.6	445	36.1
Non-Hodgkin lymphoma	3	7.8	203	16.4
Myelodysplastic syndrome	10	22.7	192	15.6
Acute lymphocytic leukemia	5	11.4	110	8.9
Allogeneic HCT-specific Parameters	N = 44		N = 1235	
Myeloablative conditioning	21	47.7	402	32.6
Reduced-intensity conditioning	23	52.3	833	67.4
Source of hematopoietic cells				
Peripheral blood	33	75.0	1070	86.6
Bone marrow	9	20.5	108	8.7
Cord blood	2	4.5	57	4.6
Allogeneic donor characteristics				
Matched-related donor	13	29.5	375	30.4
Matched-unrelated donor	22	50.0	656	53.1
Mismatched donor	9	20.5	204	16.5
GVHD Prophylactic regimens				
MTX and tacrolimus	15	34.1	451	36.7
MTX, tacrolimus, and sirolimus	12	27.3	365	29.7
Sirolimus and tacrolimus	10	22.7	235	19.1
Other	7	15.9	184	14.9
Acute GVHD	22	50.0	528	42.8

Abbreviations: GVHD, graft-versus-host disease; HCT, hematopoietic cell transplant; LTBI, latent tuberculosis infection; MTX, methotrexate.

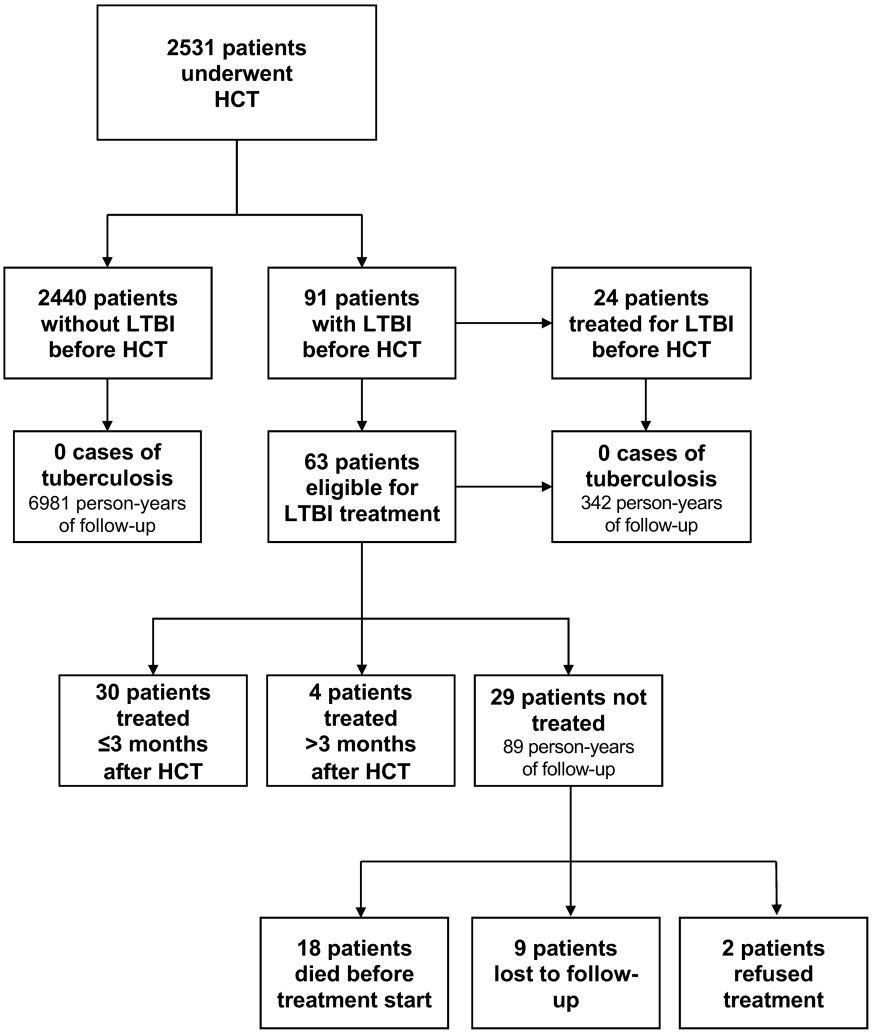

Figure 1. Summary of latent tuberculosis infection outcomes of all patients who received hematopoietic cell transplants at Dana-Farber Cancer Center from January 2010 through January 2015. See text for details. Abbreviations: HCT, hematopoietic cell transplant; LTBI, latent tuberculosis infection.

Among these 63 patients, 30 (47.6%) were treated within 3 months of HCT, including 9 patients (30.0%) who started within 28 days of transplant. Of the other patients, 4 (6.3%) initiated treatment later than 3 months post-HCT, and 29 (46.0%) did not receive treatment for reasons including physician deferral (n = 24), death within 90 days from HCT (n = 3), and patient refusal (n = 2). Treatment regimens included isoniazid (n = 29), levofloxacin (n = 4), or rifampin (n = 1). The median duration of treatment was 197 days (range, 7–326). Of the 24 patients with deferred treatment, 15 died of other causes before LTBI treatment could be initiated.

There were no cases of active tuberculosis in the cohort of patients with LTBI throughout the duration of the study, resulting in an incidence rate of 0% (95% confidence interval [CI], 0.0–1.07 cases/100 person-years) from a combined 342 person-years of follow-up. Specifically, no cases were identified in 63 patients who required LTBI therapy post-HCT (95% CI, 0.00–1.66 cases/100 person-years), including in 29 patients who did not receive preventative treatment (95% CI, 0.00–4.06/100 person-years). There were no cases of tuberculosis in the rest of the cohort either, resulting in an incidence rate of 0% (95% CI, 0.0–0.05 cases/100 person-years) from a total follow-up period of 6981 person-years.

DISCUSSION

The cumulative incidence of tuberculosis among HCT recipients in areas of high endemicity who do not use preventative therapy is between 1% and 4% [6–8]. However, the risk of reactivation is highest within the first 2 years of exposure. Furthermore, these rates likely reflect both LTBI reactivation and de novo infection. Our study suggests that the risk of developing active tuberculosis after HCT is lower in nonendemic settings. We found no cases of clinical disease among 2531 HCT recipients at our institution, including among patients who remained immunosuppressed due to post-transplant events such as GVHD and glucocorticoid treatment. Furthermore, there were no cases of

tuberculosis in the peri-transplant period among patients with untreated LTBI who waited several weeks before initiating preventative therapy.

There are several potential explanations for our results, including that some of these patients received, for other indications, antibacterial therapies that are also active against *M. tuberculosis*. However, we do not expect this to have occurred in most patients, as empiric treatment for febrile neutropenia at our institution consists of either ceftazidime or cefepime.

Reactivation of untreated LTBI occurs at an estimated rate of 0.1% per year in the general population [9], but it is expected to be more frequent in our study population. However, relative to the low rate of LTBI reactivation, the duration of severe immunosuppression peri-HCT can be short. It is also notable that, prior to undergoing HCT, most patients had previously received immunosuppressive therapy for a hematologic malignancy and did not reactivate at that time. Stability of LTBI during a prior period of severe immunosuppression suggests either the absence of residual infection [10] or the presence of durable antituberculous immunity that may persist after HCT.

Our results must be interpreted in the context of the study characteristics. Although the majority of patients who tested positive on LTBI screening were born in countries with higher tuberculosis prevalence, supporting that these screening tests represent true-positives, there is also a risk of false-positive tests when routine screening is applied to a large population. Although our data cannot be extrapolated to areas of higher tuberculosis endemicity, our results are informative on the risk of LTBI reactivation in a low endemic setting. Finally, as data collection was obtained from medical record review, we could not determine if cases of tuberculosis were diagnosed outside of our center, although we regularly follow our post-HCT population long-term.

Although LTBI therapy remains an important consideration in this patient population, our data suggest that *M. tuberculosis* reactivation does not necessarily occur immediately post-HCT. These data suggest that LTBI therapy could be deferred in the immediate post-HCT setting and initiated once patients have a lower risk of hepatotoxicity. Our data also highlight the opportunity for quality improvement with regards to the management of HCT recipients with LTBI, as several eligible patients did not receive timely preventive therapy. However, the optimal timing to start LTBI therapy and the minimum duration of treatment in this population remain undefined. Newly validated methods of interpreting currently available test results could identify those at highest risk of reactivation [11] and help determine the urgency in administering preventative therapy.

Notes

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