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Evaluation of a routine screening program with tuberculin skin testing on rates of detection of latent tuberculosis infection and prevention of active tuberculosis in patients with multiple myeloma at a Canadian cancer centre

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ABSTRACT

Background Chemotherapy-induced T cell dysfunction, resulting from treatment of multiple myeloma (MM), enhances the risk for reactivation of latent tuberculous infection (LTBI). However, routine screening for LTBI has its limitations. The objective of the present study was to assess the number of patients treated for LTBI both before and after the introduction of a consistent tuberculin skin test (TST) screening program for patients with MM at our cancer centre.

Methods This retrospective observational study analyzed adult patients with MM treated with autologous hematopoietic stem-cell transplantation from 1 January 2013 to 31 December 2014, for whom TST was consistently performed at our cancer facility. Baseline demographic characteristics of patients who received TST testing and LTBI therapy were compared with those of a pre-intervention cohort of patients (1 January 2008 to 31 December 2009) who were not tested.

Results During the post-intervention period, 170 patients with MM had a TST. In 14 patients (8.2%) results were positive, and 11 of the 14 received LTBI therapy. Of another 12 patients with radiographic imaging changes consistent with prior granulomatous disease and negative TST results, 2 were treated. No cases of tuberculosis (TB) reactivation were noted in individuals who completed LTBI therapy. One case of active TB was diagnosed in a patient with a negative TST. In contrast, in the pre-intervention matched cohort of 170 patients, no TSTs were performed, and no cases of active TB were documented.

Conclusions Patients with MM could benefit from a consistent TST testing policy coupled with subsequent LTBI therapy. However, universal testing might not be required. A targeted program combining evaluation of host risk factors, imaging findings, and screening tests might optimize LTBI diagnosis and management, and thus be effective in preventing the development of active TB in at-risk patients with MM.

Key Words Tuberculin testing, latent tuberculosis

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BACKGROUND

Mycobacterium tuberculosis (TB) complex organisms possess the property of latency and can remain inactive in exposed patients, kept in check by intact cellular immunity[1]. However, despite variable periods of dormancy, TB can be reactivated by immunosuppression and other predisposing medical conditions.

In 2017, the estimated rate of TB in Canada was 5.2 cases per 100,000 population[2]. Although the TB rate in Canada is low, Canadian-born Indigenous peoples and foreign-born individuals are disproportionately affected[3].

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Patients with hematologic malignancies are thought to be at an increased risk of developing reactivation of latent TB infection (LTBI)[4]. The *Canadian Tuberculosis Standards* guideline[5] recommends that "patients with all types of hematologic malignancies and bone marrow transplant for hematologic malignancy should be offered screening for LTBI." However, routine screening has limitations, including the risk of false-positive results and unnecessary therapy with medications that can produce significant side effects. As a result, the optimum strategy for screening for LTBI in patients with hematologic malignancies has yet to be determined.

Princess Margaret Cancer Centre (PMCC) is the only centre in the Greater Toronto Area performing autologous hematopoietic stem-cell transplantation (ASCT) for patients with multiple myeloma (MM). Before 2010, patients with MM who were to undergo ASCT were screened for LTBI on a sporadic basis, predicated on patient risk factors for a possible LTBI and clinician awareness. In 2010, our centre instituted a routine screening program for LTBI in patients with MM and other hematologic malignancies. A dedicated nurse carries out tuberculin skin testing (TST) placement and reading for patients scheduled to undergo therapy for their malignancy.

The primary objective of the present study was to assess the rate of treatment for LTBI in a pre-intervention and a post-intervention period after the introduction of routine TST screening for patients with MM undergoing ASCT. The secondary objectives were to evaluate the rate of therapy completion for LTBI in the pre- and post-intervention periods, to assess the rate of active TB in the pre- and post-intervention periods (TB infectious complications), and to evaluate medication-related side effects from treatment for LTBI.

METHODS

Patient Population

This retrospective observational cohort study assessed adult patients (≥18 years of age) who underwent ASCT for MM at PMCC during one of the two study periods and who had a TST in which the purified protein derivative (5 tuberculin units) was placed and read before transplantation. Patients were excluded if they had previously been treated for active TB, if they did not have a TST, or if a TST was placed but not read. Additionally, patients were excluded if they had previously undergone ASCT, if they had an indication for ASCT other than MM (such as lymphoma or amyloidosis), if they underwent transplantation at a centre other than PMCC, or if they had less than 1 month of post-transplantation follow-up time documented in their electronic medical record. The study was reviewed and approved by the research ethics board of the University Health Network.

The study included a 2-year post-intervention period (that is, from January 2013 to December 2014 when screening became routine) and a pre-intervention period (January 2008 to December 2009 when screening was sporadic). The historical control cohort (170 patients) was selected from a list provided by the transplantation program of patients with MM who underwent ASCT during the pre-intervention period. Each patient who underwent ASCT was assigned a study number, and a random number generator was used to select the 170 included patients. Patients in the pre-intervention period included patients screened for LTBI at the discretion of their oncologist and others who underwent no testing for LTBI. In the event of a patient meeting any exclusion criterion, the next sex-matched patient from the cohort was included instead. Follow-up data for the development of active TB was obtained for both the pre- and post-intervention cohorts for 1 year after ASCT.

Data for the following variables were also collected: patient age and sex; country of origin; Indigenous Canadian status; underlying diagnosis; comorbidities predisposing to TB reactivation; and chemotherapy received. Patient were stratified based on their lymphocyte counts ($\geq 1.0\times10^9$ vs. $<1.0\times10^9$); result of TST and size of induration; availability of interferon γ release assay testing instead of TST or in addition to TST; chest imaging findings based on chest radiography or chest computed tomography imaging; previous treatment for TB (whether therapy for LTBI therapy was initiated, and if so, with what regimen); completion of prescribed LTBI therapy; reason LTBI therapy was stopped if therapy was not completed (toxicity, compliance, etc.); and whether the patient developed active TB either during or after LTBI therapy.

A case of LTBI was defined if a patient without active TB (based on history, physical examination, and radiologic and microbiologic testing) had a 5-tuberculin-unit TST placed, with subsequent induration of 10 mm or greater. Chest imaging findings had to be consistent with prior granulomatous disease, included calcified granuloma, upper lobe fibrosis, calcified lymph nodes, and pleural thickening. Because no official definition has been codified for a high-risk compared with an intermediate- or low-risk TB incidence country, a country was considered to be high-incidence for TB if the incidence rate was 40 or more cases per 100,000 population annually.

The PMCC institutional protocol for induction antineoplastic chemotherapy in MM was the CyBorD regimen (cyclophosphamide–bortezomib–dexamethasone), followed by stem-cell mobilization and ASCT, as has been published elsewhere[6].

The post-intervention cohort was compared with the pre-intervention cohort for any significant demographic differences by chi-square test (for categorical variables) or the Student *t*-test (for continuous variables) in the GraphPad Prism software application (version 7.04: GraphPad Software, La Jolla, CA, U.S.A.). Statistical significance was established at a p value of 0.05 or less.

RESULTS

In the post-intervention cohort (patients who underwent TST testing during 2013–2014), 220 patients who had a TST were identified. After 50 patients were excluded because of prior ASCT (n = 20), an alternative baseline diagnosis (n = 18), not having undergone ASCT (n = 9), or having less than 1 month of follow-up after transplantation (usually because of transfer to another institution shortly after stem-cell infusion, n = 3), 170 patients remained for analysis. Table I describes the baseline demographic and clinical characteristics of the cohorts.

TABLE I Baseline demographic and clinical characteristics

Variable	Study cohort		*p* Value
	Pre-intervention	Post-intervention	
Patients *(n)*	170	170	
Mean age (years)	57.61±8.45	58.76±8.00	0.2
Sex [*n* (%) men]	93 (54.7)	97 (57.1)	0.6622
Birthplace [*n* (%)]			
Outside of Canada	58 (34.1)	79 (46.5)	0.0202
In a TB endemic country	23 (13.5)	38 (22.4)	0.0340
Country of origin unavailable	17	22	0.3948
Risk factors for TB reactivation [*n* (%)]			
Diabetes mellitus	18 (10.6)	23 (13.5)	0.4050
Chronic renal failure	15 (8.8)	15 (8.8)	1.0
Smoking history	44 (25.9)	44 (25.9)	1.0
Alcohol misuse	12 (7.1)	2 (11.8)	0.0112
Malnutrition	1 (0.5)	0 (0)	1.0
Chemotherapy regimen *(n)*			
CyBorD	23	166	<0.0001
Dexamethasone	68	0	<0.0001
Thalidomide–dexamethasone	52	0	<0.0001
Lenalidomide–dexamethasone	1	2	1.0
Bortezomib–dexamethasone	9	0	0.0035
Bortezomib–lenalidomide	7	0	0.0147
Other	10	2	0.0353
Bortezomib-containing	39	166	<0.0001

In the post-intervention cohort, mean age was 58.7 ± 8.0 years, and 57% were men. Of those patients, 97.8% received CyBorD induction chemotherapy before transplantation. At the time of TST, 113 patients (66.4%) had a lymphocyte count greater than 1.0×10^9/L. The TST was positive in 14 patients (Table II). Of 167 patients with chest imaging results available, another 16 patients had radiographic evidence of prior granulomatous disease on either chest radiography or chest computed tomography. Of those 16 patients, 12 with positive radiographic findings (75%) had negative TST results. Notably, 5 of the 12 (42%) had a lymphocyte count of 1.0×10^9/L or greater at the time of testing. Of the patients with positive TST results, 11 were treated: 10 received a 9-month course of isoniazid, and 1 patient received moxifloxacin for 9 months. In 1 patient with a positive TST, a subsequent interferon γ release assay was negative, and the positive TST result was therefore felt to be a false positive. As a result, the patient was not treated. Of patients with a negative TST, 3 were treated for LTBI (2 based on imaging findings, 1 based on a history of prior TB exposure). Of the treated patients, 10 were documented as having completed their proposed LTBI treatment, with no adverse events reported. Notably, 1 patient in the post-intervention cohort had a negative TST in the setting of a lymphocyte count greater than 1.0×10^9/L and subsequently developed active pulmonary TB after ASCT. His history was significant for having immigrated to Canada from an endemic country, although he denied any known TB exposure.

In the pre-intervention cohort, the induction chemotherapy regimens showed greater diversity, with 30% receiving a thalidomide-based regimen and 17% receiving a bortezomib-based regimen. No patient in that cohort had a documented TST, and no patient received LTBI therapy. Radiographic findings compatible with prior granulomatous disease were documented in 22 patients (12.9%). With respect to exposures, 23 patients came from countries with a perceived intermediate-to-high burden of TB, and 17 had a documented risk factor for TB (documented TB exposure): Indigenous Canadian status, health care worker, or residence in an endemic country for a prolonged period of time. No cases of active TB were documented in the pre-intervention cohort.

The assessment of adverse events related to LTBI therapy in the 14 patients who were treated in the post-intervention period found that 10 patients completed therapy, with none experiencing any documented adverse events—particularly no hepatotoxicity (defined as an elevation in liver function tests to 5 times normal). Those patient were regularly monitored while on therapy. The remaining patients were lost to follow-up.

TABLE II Results of tuberculin skin test (TST) and radiographic findings in the post-intervention study cohort

TST result	Radiographic findings		
	Positive	Negative	Overall
TST positive	4	10	14
TST negative	12	144	156
TOTAL	16	154	170

DISCUSSION

Multiple myeloma is the 2nd most frequent hematologic malignancy, and yet there is a paucity of data describing the development of TB in patients with MM. Tsai *et al.*[7] studied risk factors and outcomes of active TB infection in a cohort of patients with MM treated in Taiwan. They found the incidence rate of TB to be 95.5 cases per 10,000 person–years of follow-up in the MM cohort, which was significantly higher than the rate of 32.9 cases per 10,000 person–years in a matched non-MM cohort. In addition, they demonstrated that the risk of mortality in patients with MM who developed TB was twice that of patients with MM but without TB. Thus, TB could significantly affect mortality in patients with MM.

The mechanisms of immune control of TB are not fully understood, but likely involve T helper cells, particular CD4 T cell production of interferon γ, tumour necrosis factor α, and interleukin 2[8]. The chemotherapy used for the treatment of MM likely impairs T cell function. Glucocorticoids are well known to suppress peripheral T cell function[9]. Bortezomib is a proteasome inhibitor, and the proteasome is involved in T lymphocyte proliferation[10]. One study of T cell subpopulations in patients treated with bortezomib found an overall decline in CD4+ T cells in 77% of patients and CD4+ counts less than 200/mL^2 in one third of patients[11]. It has been shown clinically that impaired T cell function is a significant risk factor for developing active TB. Silva *et al.*[12] identified the following factors to be associated with the risk of TB developing in patients with hematologic malignancy: malnutrition, use of fludarabine, use of corticosteroids, and underlying malignancies that cause significant impairment to T cell–mediated immunity. It can therefore be concluded that the MM population is a patient population at increased risk for developing active TB. In our post-intervention cohort, 14 patients were treated for LTBI: 13 with isoniazid and 1 with moxifloxacin. None of those patients developed active TB.

It was surprising that we did not see any cases of active TB in the pre-intervention cohort. That observation might have been related in part to the more frequent use of thalidomide during that period. Thalidomide works by stimulating T cells and has been studied as an adjuvant treatment for TB[13]. Moreover, even though active TB is 3.5 times more likely to develop in patients with a hematologic malignancy than in the general population[14], the overall rate of active TB in Canada is low. Confounding factors affecting the seeming lack of active TB cases in the pre-intervention cohort might be related to the inclusion, in the post-intervention cohort, of an increased number of individuals born outside of Canada (46.5% vs. 34.1% in the pre-intervention cohort, $p = 0.02$) or coming from an endemic area (22.4% vs. 13.5% in the pre-intervention cohort, $p = 0.03$).

As a result of the low number of active TB cases noted in both the pre- and post-intervention cohorts, we felt that it would be most appropriate to focus our study on the frequency of treatment for LTBI. The rates of LTBI therapy completion, even among healthy patients, has been estimated to be low, ranging in previous studies from 30% to 64%[15,16]. Given concerns about polypharmacy and additive side effects, the ability or willingness on the part of patients with hematologic malignancies to complete LTBI therapy might be questioned. One study did compare 21 patients who simultaneously received LTBI and antineoplastic therapy[4] with 84 control participants who received LTBI therapy alone, finding that the two groups showed no significant differences in the rate of LTBI therapy completion. An increased rate of hepatotoxicity was observed in the group receiving antineoplastic therapy as well as LTBI; however, although 3 patients in the control group required withdrawal of their LTBI therapy because of extrahepatic complications, no patient in the group receiving antineoplastic therapy required withdrawal[4]. In contrast, as demonstrated by Ahn *et al.*[17], development of active TB often results in treatment interruptions attributable to concomitant LTBI therapy and antineoplastic chemotherapy, with subsequent decreased response to therapy and adverse outcomes for those patients. In our study, isoniazid was found to be well tolerated, without any documented episodes of hepatotoxicity, although we are missing data about therapy completion in one third of the patients.

The significance of the present study is twofold. First, it highlights changes in the demographics of patients treated for MM, with an observed increase in non-Canadian-born individuals who might be predisposed to a greater risk of LTBI. Indeed, proper infection prevention and control measures are necessary in cancer hospitals, because at least one series of health-care-acquired TB cases has been documented in U.S. patients with malignancy[18]. In that series, delayed diagnosis of TB in 2 patients with leukemia resulted in the infection with TB of 19 patients and staff at 3 hospitals and a residential facility. The authors posit that baseline screening, together with earlier recognition of clinical disease, could have prevented the outbreak. The findings in our study potentially have implications for policy-setting in cancer centres treating patients with MM.

Some limitations of our study merit consideration. The retrospective nature of the study is a key limitation. We were missing some data that were not adequately documented for non-Canadian-born individuals, such as bacille Calmette–Guérin status and potential exposures to non-tuberculous mycobacteria. Those factors might have falsely elevated the rate of TST positivity. In addition, some patients in the pre-intervention cohort (<10%) were health care workers and would likely have been receiving routine TSTs at their place of employment. Unfortunately, that information was not captured by the treating health care personnel. Also, given the lack of power presented by the size of our cohorts, cases of active TB were insufficient to draw any meaningful conclusions about the utility of LTBI screening.

CONCLUSIONS

Our study is the first to look at the effect of a routine screening program on rates of detection and outcomes of therapy for LTBI in the MM population. Our study demonstrated that, although routine TSTs increased the number of cases of LTBI detected, TSTs alone are probably inadequate to detect all cases of LTBI. Moreover, routine TSTs likely consume considerable resources that would appear to be unnecessary in a low-burden country such as Canada. A targeted program combining evaluation of host risk factors, diagnostic

imaging findings, and screening tests that could include TSTs and interferon γ release assay testing might optimize LTBI diagnosis and management. However, further studies are needed to validate such an approach.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none pertaining to the subject matter presented here.

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