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Risk and impact of tuberculosis in patients with chronic myeloid leukemia: A nationwide population-based study in Taiwan

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The relationship between chronic myeloid leukemia (CML) and tuberculosis (TB) has not been determined. We conducted a national survey including 1,082 CML patients identified from the Taiwan National Health Insurance database covering a period between 1998 and 2011; the matched non-exposed cohort included 10,820 subjects without CML that were matched for age, sex and comorbidities. The impact of TB was measured by the overall mortality, and the risk factors were identified by a multivariate Cox proportional hazards model. We found the risk of TB was higher in the CML cohort, with an adjusted hazard ratio (aHR) of 3.76 ($p = 0.001$) for both pulmonary (aHR 3.23, $p < 0.001$) and extrapulmonary (aHR 9.77, $p = 0.001$) TB. Specific risk factors were: aged ≥ 60 (aHR 3.24, $p = 0.022$), being male (aHR 13.49, $p = 0.012$), receiving stem cell transplantation (aHR 10.50, $p = 0.001$) and interferon-α therapy (aHR 3.34, $p = 0.011$). CML patients with TB had a higher mortality rate than those without (aHR 2.04, $p = 0.043$). We conclude that the incidence of TB is significantly higher in CML patients of male sex, aged ≥ 60, having received either stem cell transplantation or interferon-α treatment. Careful screening strategies for TB should be considered for CML patients with high risk of the infection.

Chronic myeloid leukemia (CML) is a hematologic malignancy driven by unregulated tyrosine kinase signaling. The disease develops from a single, pluripotent, hematopoietic stem cell acquiring the BCR-ABL fusion gene, which results in a proliferative advantage.[1] An annual CML incidence of 12/1,000,000 in the Taiwanese population was recently reported.[2] Although the incidence of this disease is low, the advent of effective therapy with tyrosine kinase inhibitors (TKIs) has remarkably improved outcomes for CML patients. With TKIs that inhibit the BCR-ABL fusion gene product, survival of CML patients has dramatically improved over the past decade. Thus, significant attention should be paid to possible long-term complications related to defective neutrophil function.

Tuberculosis (TB) is a devastating pathology, responsible for 1.7 million deaths worldwide per year, which amounts to three deaths each minute.[3] It is endemic in southeastern Asia, as well as Taiwan. In 2004, the incidence of TB among the general Taiwanese population was 7.41/10,000 with a mortality rate of 0.42/10,000.[4] TB can develop from transmission by actively infected persons or reactivation of a quiescent infection. Suffering from impaired immunity, patients with CML may be at greater risk of developing active TB.[5–7]

Key words: BCR-ABL tyrosine kinase inhibitors, chronic myeloid leukemia, extrapulmonary tuberculosis, hematopoietic stem cell transplantation, imatinib, pulmonary tuberculosis
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Epidemiology

What's new?

Patients with chronic myeloid leukemia (CML) are immunosuppressed but their risk of developing active tuberculosis has not been assessed. This study from Taiwan using a nationwide population-based dataset demonstrates that the incidence of tuberculosis is significantly higher in patients with CML (adjusted hazard ration of 3.76), especially in those of male sex, older age and receiving either stem cell transplantation or interferon-α treatment. Treatment with tyrosine kinase inhibitors did not increase the risk. The authors recommend intensified tuberculosis screening in CML patients, especially those with increased risk.

In addition, concurrent treatment for TB and CML faces many clinical challenges, including drug–drug interactions, drug toxicities and a high pill burden. For example, CML patients with TB might need a higher dose of imatinib than CML patients without TB to overcome the potential induction of the CYP3A enzyme by rifampicin to reach the ideal therapeutic potency.[8–10] However, a higher dose increases the risk of drug side effects, which can reduce patient adherence. The relationship between CML and TB has been reported in only anecdotal case observations.[11] The largest CML case series published to date reports the cases of only three patients who developed active TB after a median of 17 months of imatinib therapy.[12] The association between TB, CML and related therapies deserves more extensive investigation.

The National Health Insurance (NHI) program of Taiwan provides comprehensive coverage. It offers an excellent opportunity to investigate epidemiology and the association between CML and TB. We conducted a nationwide population-based cohort study to analyze data from the National Health Insurance Research Database (NHIRD). The aim was to clarify the incidence rate, sites of involvement, risk factors and long-term outcome of TB in CML patients.

Material and Methods

Data sources

The NHI program was initiated by the Taiwanese government in 1995 to provide comprehensive health care for all of its residents. Enrollment in this program is mandatory and the proportion of the insured population is >99%. The NHI program provides comprehensive medical care that includes outpatient, inpatient, emergency, dental, prescription drug and traditional Chinese medicine services. Information from multiple NHI databases (*e.g.*, NHI enrollment files, claims data and a prescription drug registry) are managed and publicly released by the National Health Research Institutes, Taiwan. These databases provide comprehensive utilization and enrollment information for all patients with catastrophic illnesses who are exempted from copayments under the NHI program. Patients with CML and non-exposed control subjects were identified from the NHI database. All information that may potentially identify any individual patient is encrypted. The confidentiality of the patient data stored in the registry is guaranteed by the data regulations of the Bureau of National Health Insurance and the National Health Research Institutes. This study was approved by the institutional review board of Taipei Veterans General Hospital (2012-12-001AC).

Study population

We conducted a retrospective cohort study from January 1, 1998 to December 31, 2011. Using the discharge codes (205.1X) in the *International Classification of Diseases, 9th revision, and The Clinical Modification (ICD-9-CM)* of the Registry of Catastrophic Illness. Patients who were newly diagnosed with CML between January 1, 1998 and December 31, 2011 were enrolled. CML diagnosis was confirmed by patients having been prescribed BCR-ABL TKIs. Payment of the first-generation BCR-ABL TKI, imatinib, has been covered by the National Health Insurance since 2002. Because of the high cost of BCR-ABL TKIs, prescription of these drugs requires peer review to confirm the diagnosis based on laboratory data. The peer-review process includes cytological and pathological findings in bone marrow samples, cytogenetic analyses, and molecular analyses of the BCR-ABL fusion gene. Because Taiwan's national insurance covered imatinib as a second-line CML therapy before 2004, it was possible to evaluate the TB risk before and after BCR-ABL TKI treatment. TB infection is categorized as pulmonary and extrapulmonary TB according to WHO criteria.[13] Diagnosis of TB includes laboratory and clinical diagnosis that is defined by a compatible ICD-9-CM code (010–018).[13] We used a prescription of at least two anti-TB medications for ≥28 days to confirm the diagnosis.[8] We focused on TB incidence in adult patients with CML. Patients who were under 20 years of age or had antecedent TB were excluded from the study. Information on comorbidities and therapeutics, such as hematopoietic stem cell transplantation (HSCT), interferon-α and BCR-ABL TKIs (*i.e.*, imatinib, dasatinib and nilotinib) were collected for further analysis.

Control cohort

Subjects without CML were used as the matched cohort and were randomly selected from 1,000,000 NHI beneficiaries out of a population of 21,400,826 enrollees throughout Taiwan in 2000. Because both CML and TB are rare diseases, each CML patient was matched with 10 non-CML subjects by age, sex and presence of comorbidities on the same index date of diagnosis.[14] The same exclusion criteria were applied to the

matched cohort. A total of 10,820 subjects comprised the matched non-exposed cohort for comparison.

Statistical analyses

The main dependent variable was incident TB occurrence. The two cohorts were followed until the occurrence of TB, death, or the end of the study period (2011). Each subject was followed for a maximum of 14 years. Formal comparisons between groups were made using χ^2 tests for categorical variables. The Kaplan-Meier method was employed for estimation of cumulative incidence. A Cox proportional hazards model was used to compute the hazard ratios (HRs) and accompanying 95% confidence intervals (CIs) after adjustment for confounders. The multivariate Cox proportional hazards model was used to identify risk factors for TB. The proportional hazards assumption was tested by Schoenfeld residuals before using the model. Control variables such as age, sex, comorbidities and therapeutic strategies were included in the model. Those with $p < 0.1$ in the univariate model were used in the multivariate analysis. In addition, age and sex were forced into the multivariate analysis because they may confound between-subject comparisons. Therapeutic strategies after CML diagnosis were treated as time-dependent variables to prevent immortal time bias. Although all CML patients received at least one type of BCR-ABL TKIs, we estimated the hazard functions of TB risk in CML patients before and after BCR-ABL TKIs and calculated adjusted HRs using a Cox proportional hazards model. We assessed goodness of fit or discriminatory ability for Cox model using Harrell's concordance statistic (c-statistic).[15] Extraction and computation of data were performed using the Perl programming language (version 5.12.2). Microsoft SQL Server 2005 (Microsoft, Redmond, WA) was used for

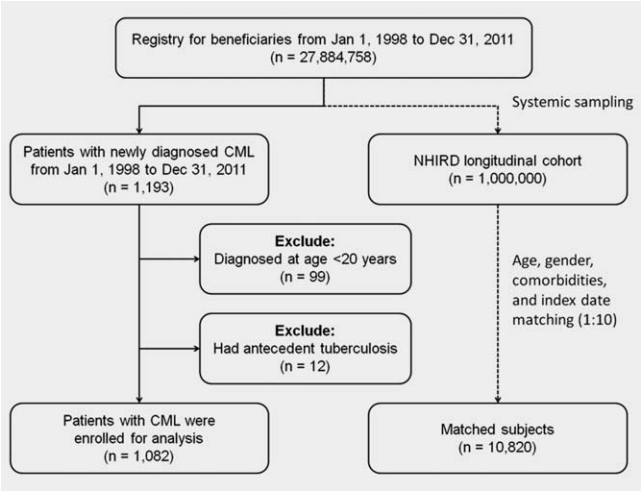

Figure 1. Flow chart for patient selection.

Table 1. Basic characteristics of patients with chronic myeloid leukemia and the matched cohort

Characteristics	Patients with CML ($n = 1,082$)		Matched cohort ($n = 10,820$)		p value
	n	(%)	*n*	(%)	
Median age, years (interquartile range)	48 (36–60.5)		48 (36–60.5)		
Age, years					
<60	800	(73.9)	8000	(73.6)	1.000
≥60	282	(26.1)	2820	(26.1)	
Sex					
Female	430	(39.7)	4300	(39.7)	1.000
Male	652	(60.3)	6520	(60.3)	
Comorbidity					
Diabetes mellitus	243	(22.5)	2426	(22.4)	0.978
COPD	221	(20.4)	2207	(20.4)	0.983
Asthma	153	(14.1)	1532	(14.2)	0.987
ESRD	40	(3.7)	405	(3.7)	0.939
Liver cirrhosis	44	(4.1)	394	(3.6)	0.479
Autoimmune diseases	72	(6.7)	717	(6.6)	0.972
Treatment					
HSCT	49	(4.5)			
Interferon-α	252	(23.3)			
BCR-ABL TKIs	1,082	(100.0)			

Abbreviations: BCR-ABL TKIs, BCR-ABL tyrosine kinase inhibitors (including imatinib, dasatinib, and nilotinib); CML, chronic myeloid leukemia; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; HSCT, hematopoietic stem cell transplantation.

data linkage, processing, and sampling. All statistical analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC) or STATA statistical software (version 12.1; StataCorp, USA). A $p < 0.05$ was considered to be statistically significant.

Results

Clinical characteristics of the study population

During the 14-year study period, a total of 1,193 patients with newly diagnosed CML were identified. Figure 1 shows the flowchart for patient recruitment. After excluding patients who were diagnosed with CML at younger than 20 years of age ($n = 99$) or had antecedent TB ($n = 12$), 1,082 patients were enrolled for analyses. The study subjects were predominantly male (60.3%) and the median age was 48 years (interquartile range, 36–60.5 years). Diabetes mellitus (DM; 22.5%) and chronic obstructive pulmonary disease (COPD; 20.4%) were the most common comorbidities. Demographic characteristics and comorbidities of the CML and matched cohorts (1:10) are shown in Table 1. Comparison subjects were matched according to age, sex, and all listed comorbidities. The median follow-up time was 3.90 years for the CML cohort and 4.68 years for the matched cohort.

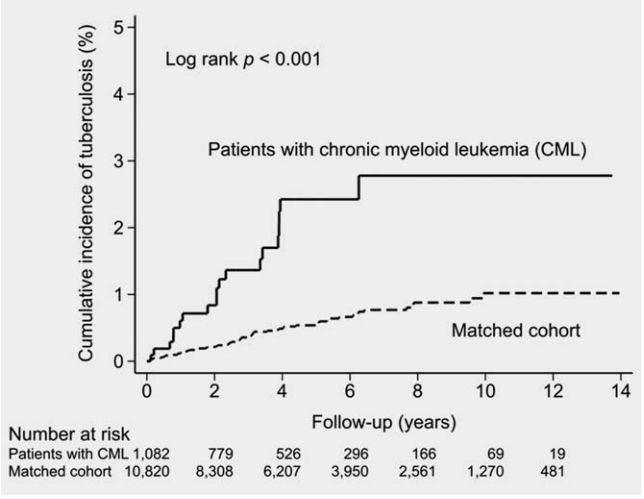

Figure 2. The cumulative incidence of tuberculosis (TB) in patients with chronic myeloid leukemia (CML) and the matched cohort.

Comparison of the incidence rates of TB between patients with CML and the matched cohort

Kaplan–Meier estimates showed that the cumulative incidence of TB was significantly higher in the CML cohort than in the matched cohort (log-rank test; $p < 0.001$) (Fig. 2). Of 11,902 patients, 78 (0.7%) were diagnosed with TB. Nineteen (1.8%) of these patients were from the CML cohort and 59 (0.6%) were from the matched cohort (Table 2). The incidence rate of TB was 40.1 per 10,000 person-years of follow-up in the CML cohort and 10.5 in the matched cohort. After adjustment for age, sex, and all comorbidities listed in Table 1, the CML cohort had a greater overall risk of developing TB (adjusted HR 3.76, 95% CI 2.24–6.31, $p < 0.001$). Furthermore, CML patients had increased risk for both pulmonary TB (adjusted HR 3.23, 95% CI 1.82–5.73, $p < 0.001$) and extrapulmonary TB (adjusted HR 9.77, 95% CI 2.61–36.59, $p = 0.001$).

Risks factors for TB in patients with CML

The multivariable Cox proportional hazards analysis indicated that the following variables were statistically significant: ≥60 years of age (HR 3.24, 95% CI 1.19–8.83, $p = 0.022$), male sex (HR 13.49, 95% CI 1.79–101.54, $p = 0.012$), liver cirrhosis (HR 4.30, 95% CI 0.97–19.05, $p = 0.055$), HSCT (HR 10.50, 95% CI 2.77–39.80, $p = 0.001$), and interferon-α therapy (HR 3.34, 95% CI 1.32–8.47, $p = 0.011$) (Table 3). To investigate whether TB in CML patients was associated with HSCT, TB incidence in CML patients without or before HSCT was further analyzed. We found that CML patients still had a greater risk of developing TB even without exposure to HSCT (adjusted HR 3.23, 95% CI 1.86–5.62, $p < 0.001$) (Supporting Information Table 1). Of note, CML did not increase the risk of TB after treatment with BCR-ABL TKIs (HR 0.51, 95% CI 0.19–1.38, $p = 0.184$). The incidence of TB in CML patients and matched cohort patients over different time periods are shown in Supporting Information Figure 1.

Table 2. Incidence of pulmonary and extrapulmonary tuberculosis in patients with chronic myeloid leukemia and the matched cohort

	Patients with CML ($n = 1,082$)		Matched cohort ($n = 10,820$)					
Sites of TB involvement	TB numbers	Per 10,000 person-years	TB numbers	Per 10,000 person-years	Crude HR (95% CI)	p value	Adjusted[1] HR (95% CI)	p value
Total	19	40.1	59	10.5	3.65 (2.18–6.12)	<0.001	3.76 (2.24–6.31)	<0.001
Pulmonary TB	15	31.7	54	9.6	3.14 (1.77–5.57)	<0.001	3.23 (1.82–5.73)	<0.001
Extrapulmonary TB	4[1]	8.5	5	0.9	9.18 (2.46–34.21)	0.001	9.77 (2.61–36.59)	0.001

Adjusted for age, gender, and comorbidities listed in Table 1.
[1]Three of them had tuberculous pleurisy and the other one had tuberculosis of mediastinum.
Abbreviations: CI, confidence interval; CML, chronic myeloid leukemia; HR, hazard ratio; TB, tuberculosis.

Table 3. Risk factors for tuberculosis in patients with chronic myeloid leukemia

	Univariate analysis		Multivariate analysis[1]	
Variables	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age ≥60 years	2.04 (0.80–5.18)	0.136	3.24 (1.19–8.83)	0.022
Male sex	12.42 (1.66–92.93)	0.014	13.49 (1.79–101.54)	0.012
Comorbidity				
Diabetes mellitus	1.09 (0.36–3.28)	0.883		
COPD	0.84 (0.25–2.89)	0.782		
Asthma	0.87 (0.20–3.78)	0.856		
ESRD	0.00 (0.00–)	0.989		
Liver cirrhosis	3.82 (0.88–16.60)	0.074	4.30 (0.97–19.05)	0.055
Autoimmune diseases	0.88 (0.12–6.56)	0.897		
Treatment[2]				
HSCT	6.79 (1.94–23.77)	0.033	10.50 (2.77–39.80)	0.001
Interferon-α	2.76 (1.11–6.90)	0.030	3.34 (1.32–8.47)	0.011
BCR-ABL TKIs	0.51 (0.19–1.38)	0.184		

[1]All factors with $p < 0.1$ in univariate analysis were included in the Cox multivariate analysis, and age was entered in the Cox multivariate analysis.
[2]Treatment was analyzed as a time-dependent covariate in the Cox regression model.
Abbreviations: BCR-ABL TKIs, BCR-ABL tyrosine kinase inhibitors (including imatinib, dasatinib, and nilotinib); CI, confidence interval; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation.

Table 4. Risk factors for mortality in patients with chronic myeloid leukemia

	Univariate analysis		Multivariate analysis[1]	
Variables	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Tuberculosis[2]	2.62 (1.33–5.15)	0.006	2.04 (1.02–4.08)	0.043
Age ≥60 years	1.95 (1.46–2.60)	<0.001	1.87 (1.39–2.50)	<0.001
Male sex	1.45 (1.08–1.94)	0.015	1.44 (1.07–1.94)	0.017
Comorbidity				
Diabetes mellitus	1.32 (0.95–1.84)	0.100		
COPD	1.22 (0.86–1.73)	0.260		
Asthma	1.08 (0.70–1.68)	0.720		
ESRD	2.35 (1.34–4.12)	0.003	1.98 (1.12–3.51)	0.019
Liver cirrhosis	2.18 (1.24–3.83)	0.007	1.94 (1.10–3.42)	0.023
Autoimmune diseases	1.01 (0.55–1.86)	0.964		

[1]All factors with $p < 0.1$ in univariate analysis were included in the Cox multivariate analysis.
[2]Tuberculosis was analyzed as a time-dependent covariate in the Cox regression model.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; HR, hazard ratio.

Analysis of clinical correlates and long-term outcomes of TB

Among the 1,082 patients with CML, 202 (18.7%) died during the study period. CML patients with TB had a higher mortality rate than those without TB (adjusted HR 2.04, 95% CI 1.02–4.08, $p = 0.043$; Table 4).

Discussion

This nationwide population-based study demonstrates that the 1,082 patients with CML had a significantly greater risk of developing intrapulmonary and extrapulmonary TB (HR 3.76) compared to the 10,820 matched controls during the 14-year study period. The increased risk of TB infection could be attributed to some CML-related therapies, but was not associated with BCR-ABL TKIs. Moreover, our study shows that CML patients with TB have an increased risk of death compared to those without TB. The findings of this study provide a reliable and objective analysis of TB in patients with CML because of the large sample size, strict diagnostic criteria, and unbiased subject selection. Since the certification of an NHI-defined catastrophic illness such as CML can exempt patients from related medical expenses, the government has implemented a strict verification process. For CML, the catastrophic illness certificate is granted based on

medical records and laboratory results such as cytological and pathological findings from bone marrow samples, cytogenetic analyses, and molecular analyses of the BCR-ABL fusion gene. Moreover, physicians in Taiwan are legally required to report TB cases (including deaths) to the Centers for Disease Control (CDC) within one week. The CDC can punish physicians who violate this law under the Infectious Disease Control Act.[16] This oversight makes it unlikely that any diagnosed cases of TB were not documented in the NHIR database. Additionally, a special committee composed of TB experts reviews the diagnosis of any reported TB cases to avoid an inappropriate diagnosis that would expose the patient to unnecessary toxicity from anti-TB medications. Altogether, the diagnoses of CML and TB in our study were reliable and exhaustive.

CML is a relatively rare disease,[17] and only a small proportion of patients with CML develop TB. Because of its rarity, patients with CML identified in this database were matched with control subjects at a ratio of 1:10.[14] Our population-based study demonstrates that the incidence of TB in patients with CML (40.1/10,000 person-years) was 3.76 times higher than that in the matched cohort (10.5/10,000 person-years). Moreover, CML was associated with both pulmonary and extrapulmonary TB.

Known risk factors for TB in the general population include advanced age,[18] male sex,[19] DM,[20] COPD,[21] end-stage renal disease,[22] liver cirrhosis[23] and autoimmune disease. Our study also shows that patients who were 60 or older, male were more likely to be infected with TB. Elderly patients have a particularly high risk of developing TB. Age-related factors both increase the risk of TB reactivation and increase vulnerability to TB.

In some reported cases, CML treatments increased the risk of TB in patients with CML.[7] Our study shows that HSCT increases the risk of TB by nine times. Some reports have shown that HSCT, not restricted to treating CML, might increase the risk of TB development up to 13 times.[24–28] Allogeneic HSCT patients are known to have impaired cell-mediated immunity resulting from conditioning regimens, immunosuppressive agents, and graft-versus-host disease.[28]

Several studies have reported the occurrence of TB after imatinib therapy.[7,10,12,29–31] Laboratory studies have demonstrated that BCR-ABL TKIs impair T-cell activation and proliferation *in vitro*.[5,6,32,33] Two clinical studies observed hypoglobulinemia in patients receiving imatinib.[34,35] However, our study did not indicate BCR-ABL TKI use as a risk factor for TB in CML patients (HR 0.51, 95% CI 0.19–1.38, $p = 0.184$). Massimo *et al.* observed 250 CML patients between 2001 and 2006 and reported a low incidence of opportunistic and viral infections in chronic phase CML patients treated with imatinib,[36] which does not contradict our findings. Furthermore, Ruth *et al.* suggested that imatinib may have some therapeutic efficacy against TB.[37] However, escalation of imatinib dose might be needed after concomitant medication with anti-TB agents since the CYP3A enzyme could be induced by rifampicin. Federica *et al.* reported that the 50% increase in the imatinib dose might be feasible and tolerable.[8]

Rare case reports have discussed the association between TB and interferon-α therapy.[38,39] Although there is no evidence that interferon-α use would induce TB, the fever, weight loss, and anorexia associated with therapy may promote clinical manifestations of TB.[39] In our study, most patients received interferon-α prior to imatinib during the period before 2004, when the NHI of Taiwan covered imatinib as a second-line therapy in CML. Thus, it seems that patients with CML had a lower incidence of TB after switching to imatinib treatment (Supporting Information Fig. 1).

In 2004, TB was the 13th leading cause of death in Taiwan and accounted for 0.72% of all deaths. In our analysis, CML patients with TB also had significantly higher mortality rates than those without TB (adjusted HR 2.04, 95% CI 1.02–4.08, $p = 0.043$). The worse outcomes of these patients may be explained by their weakened immune systems or complications of TB.[40] Our observation suggests that diagnosis and treatment of latent TB infection is mandatory in CML patients, especially in those with risk factors for the infection. At the moment, a well-designed algorithm for latent TB diagnosis and treatment is still lacking and is urgently needed to optimize the management of CML patients.

This study has limitations. First, the key limitation is that the administrative data used in this study did not provide smoking status, socioeconomic status, performance status, phases of CML, or laboratory data including quantitative BCR-ABL results. Consequently, this study cannot examine the relationship between TB and these clinical parameters in detail. Second, we excluded patients who had antecedent TB before CML diagnosis. Although the exclusion of these patients enabled us to clarify the relationship between CML and newly diagnosed TB, it was difficult to differentiate whether TB resulted from the reactivation of old foci or represented new infections. Finally, this study included only CML patients who were treated with BCR-ABL TKIs and thus can analyze only the incidence of TB in CML patients by comparing them before and after TKI treatment. The risk of TB infection might be different in CML patients who have never been treated with TKIs. Because TB infection increases mortality in CML patients, a small number of CML patients with TB might never have had the opportunity to use BCR-ABL TKIs and would have therefore been excluded from this study. This may have caused an underestimation of the protective effects of BCR-ABL TKIs.

In conclusion, CML patients are at increased risk of developing TB. Physicians responsible for caring for these patients should be aware of this risk and vigilant about potential clinical manifestation of TB. Careful practical approaches to screening for TB in suspicious cases should be implemented. These approaches should use sputum acid-fast staining and culture, chest x-rays, and further diagnostic testing should be mandatory for these patients, especially those at the highest risk.

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