Case Report

Diseases at the Crossroads: Chronic Myelogenous Leukemia and Tuberculosis

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Abstract

Chronic myelogenous leukemia (CML) and tuberculosis (TB) are diseases with effective available therapy. Treating patients who are afflicted simultaneously with both of these conditions is challenging due to significant drug interactions and the requirement of strict adherence to the multi-agent treatment regimen. Here, we report a case of peritoneal tuberculosis which was successfully treated with a non-rifampin based regimen in tandem with ongoing administration of a tyrosine kinase inhibitor, dasatinib, for CML. We discuss treatment challenges and the strategy on how to circumvent them. As prevalence of CML increases worldwide, patients with concomitant CML and TB will be seen more often by physicians in all continents, and development of guidelines on simultaneous management of these conditions is imperative.

Keywords: Chronic myelogenous leukemia (CML), disease, tuberculosis (TB)

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Introduction

Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm that occurs as a result of a chromosomal translocation, t(9;22)(q34;q11), in hematopoietic stem cells. This translocation generates Philadelphia chromosome that contains the oncogenic *BCR-ABL* fusion gene, whose product results in increased tyrosine kinase activity in hematopoietic cells.[1] The approval of tyrosine kinase inhibitors (TKIs) such as imatinib, dasatinib and nilotinib, which safely and effectively treat CML, has culminated in the drop in annual CML-related mortality from 25% to 2% in the United States.[2] Stable incidence rate and decreased mortality rate have resulted in ever-rising CML prevalence worldwide.[3] Management of comorbid conditions in CML survivors is a growing challenge for health care professionals.

Tuberculosis (TB) is primarily caused by airborne spread of *Mycobacterium* species and has a worldwide incidence of over 8 million annually.[4] Tuberculosis alone was responsible for 1.3 million deaths worldwide in 2012, making it the second most deadly infectious disease after HIV/AIDS.[4] The treatment for active tuberculosis involves a multi-drug regimen of antimicrobials, usually including rifampin and isoniazid. Rifampin induces the cytochrome P450 enzymes and can interfere with the metabolism of many other drugs including TKIs.

There is a paucity of information with regard to the simultaneous treatment of CML and TB. Here, we present a case of a patient with CML who was diagnosed with active tuberculosis during TKI treatment. We discuss therapeutic challenges in the concurrent treatment of both diseases, and suggest guidelines that may assist physicians in their day-to-day practice of treating patients with these two highly treatable disorders.

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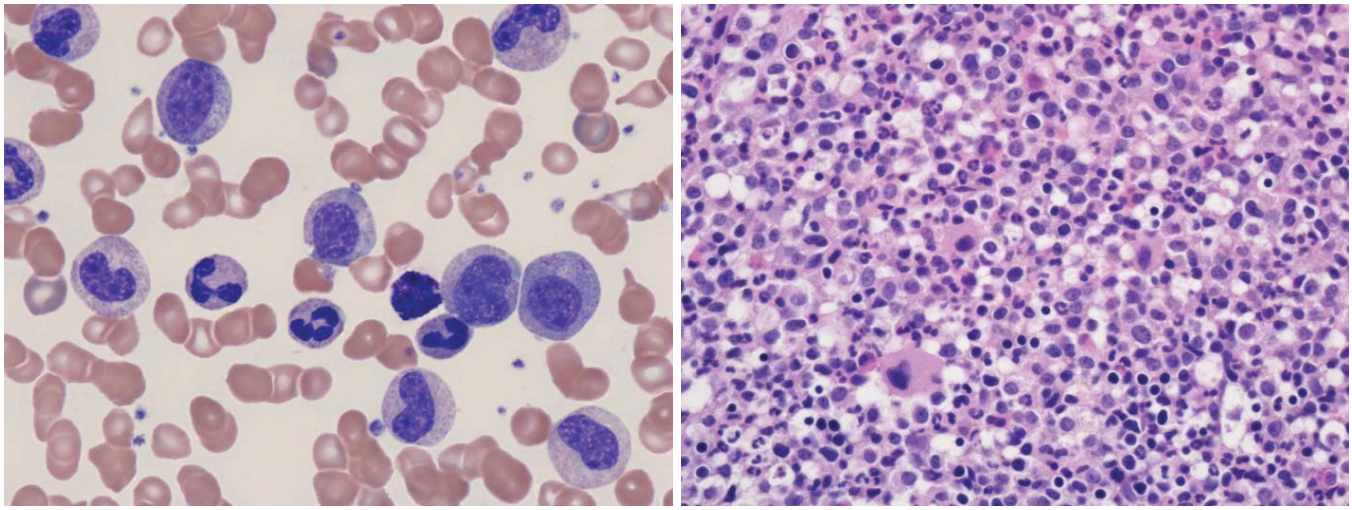
Case Report

A 29 year-old woman from Cameroon with a past medical history significant for uterine fibroids presented with menorrhagia, night sweats, and unintentional weight loss. Physical exam was notable for an enlarged spleen and uterus. Pelvic ultrasound revealed several enlarged uterine fibroids. Laboratory tests revealed a white blood cell count 105 × 10^9/L, hemoglobin 8.7 g/dL, and platelet count 443 × 10^9/L. The remaining laboratory tests were unremarkable. Her qualitative β-HCG was negative. The peripheral blood smear was significant for left shift granulocytosis with frequent basophils (Figure 1a). Flow cytometry of the peripheral blood did not reveal an increased blast population. A bone marrow biopsy revealed a hypercellular marrow with granulocytic hyperplasia and small hypolobated megakaryocytes (Figure 1b). Karyotype analysis was significant for twenty out of twenty metaphase cells with t(9;22) (q34;q11), consistent with a diagnosis of chronic phase CML. The quantitative RT-PCR assay was positive for both the b3a2 and b2a2 (p210) fusion gene transcripts at 56.65% and 0.07%, respectively, titrated to the current International Scale (IS). The patient began treatment with dasatinib 100 mg by mouth once daily. The patient's white blood cell counts normalized after ten weeks of TKI therapy however, her microcytic anemia persisted in the milieu of ongoing vaginal bleeding (Table 1).

A bone marrow biopsy after six months of treatment with dasatinib confirmed complete cytogenetic response (CCyR), as no metaphase cells were positive for *BCR-ABL* by Fluorescence In Situ Hybridization (FISH) in 200 metaphase cells. The patient's *BCR-ABL* mRNA transcript level in the peripheral blood was



a b

Figure 1. a) Peripheral blood smear, hematoxylin and eosin stain. Numerous granulocytes including promyelocyes, myelocytes, metamyelocytes and basophils; **b)** Bone marrow core, hematoxylin and eosin stain. Hypercellular marrow with granulocytic hyperplasia.

Table 1. Summary of Laboratory Testing

	WBC (K/mL)	Hemoglobin (g/dL)	Neutrophils (K/mL)	Basophils (K/mL)	Platelets (10^9/L)	b3a2 transcript	b2a2 transcript
At Diagnosis	117.4	8.3	106.5	3.5	365	56.65%	0.07%
Week +9	5.4	8.9	3	0	238	- - -	- - -
Week +13	5.1	9.6	2.8	0	118	0.75%	< 0.001%
Week +26	4.2	6.9	2.6	0	377	0.03%	< 0.001%
Week +38	4.1	11.2	2.6	0	270	0.20%	< 0.001%
Week +54	10.6	10.5	6.6	0.3	329	21.69%	0.02%
Week +62	4.9	9.1	2.6	0	215	10.37%	< 0.001%
Week +74	7.0	9.1	2.8	0	208	0.08%	< 0.001%

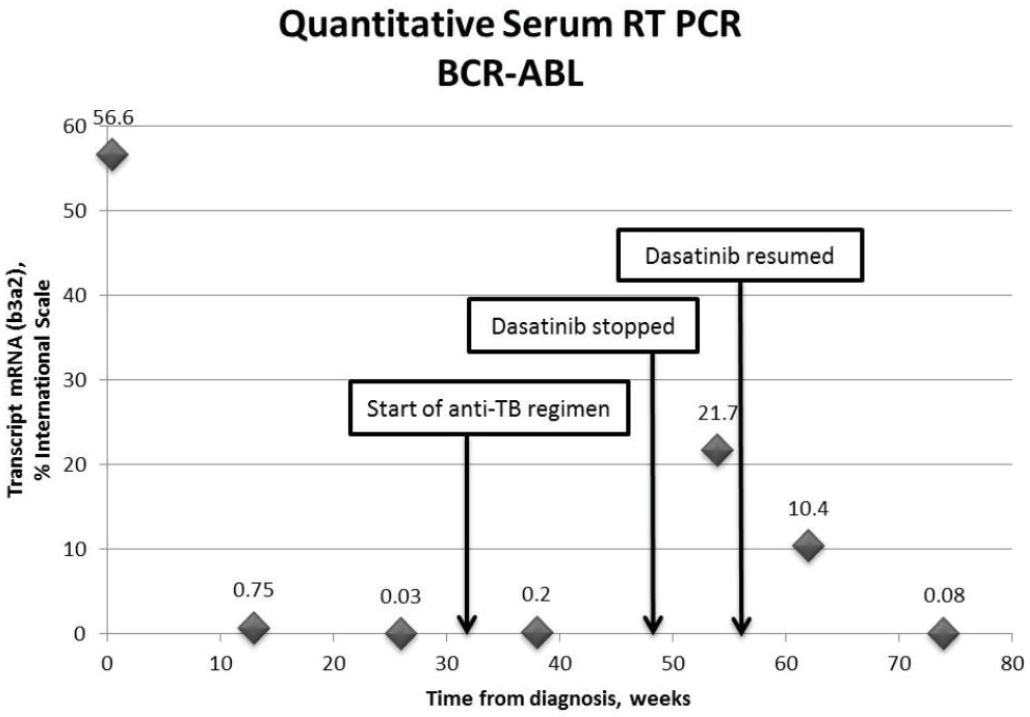


Figure 2. Summary of *BCR-ABL* mRNA transcript levels over the course of the patient's treatment course

0.03% at the six months point, meeting the criteria for a major molecular response (MMR). The patient was noted to have a further decrease in hemoglobin from baseline with a normal leukocyte and platelet counts. She required transfusion of packed red blood cells for her symptomatic anemia, and was referred to a gynecologist for management of her severe menorrhagia.

An elective myomectomy was performed weeks after attaining MMR. During her myomectomy, she was noted to have approximately 500 mL of dark peritoneal ascites and peritoneal studding. Pathologic examination of the peritoneal lesions revealed non-caseating granulomata, but a negative acid fast stain. The quantiferon gold test was positive, and the patient was diagnosed with tuberculosis. Computerized tomography (CT) scans of the chest did not reveal any adenopathy or granulomata. She was treated with isoniazid, moxifloxacin, pyrazinamide, and ethambutol. *We decided to treat her with a non-rifampin containing regimen out of concern that rifampin would interfere with the metabolism of dasatinib, upon which her CML treatment response was vitally dependent.*

Unfortunately, the patient's inability to afford dasatinib resulted in a five week interruption of her CML treatment. Subsequently, her *BCR-ABL* mRNA transcript rose to 21.69% while off dasatinib. At week 54 from diagnosis, the patient regained access to dasatinib and resumed CML treatment.

Throughout this time period, the patient had continued her anti-TB regimen without interruption through the health department's directly observed therapy program. After the initial three months of treatment with a four-drug anti-TB regimen, she was transitioned to a two-drug regimen of isoniazid and moxifloxacin.

At week 74, five months after resuming dasatinib, the patient had a *BCR-ABL* mRNA transcript of 0.08%, thereby re-establishing a major molecular response. Figure 2 summarizes the *BCR-ABL* mRNA transcript levels in the patient over the course of her treatment.

Discussion

This case illustrates the importance of maintaining therapeutic levels of TKIs for treatment of CML. The patient achieved a major molecular response with adequate therapy, despite starting a multidrug anti-TB regimen. Based on the *BCR-ABL* mRNA transcript levels, there was no significant effect of isoniazid, moxifloxacin, pyrazinamide, and ethambutol on the metabolism of dasatinib. To the best of our knowledge, this is the first reported case of a patient with CML undergoing simultaneous treatment for tuberculosis. Notably, the combination of dasatinib and anti-tuberculosis were tolerable. The TKI and non-rifampin containing regimen did not significantly interact based on the patient's treatment response, nor did the patient experience significant drug toxicities.

CML and tuberculosis share a fundamental characteristic: medication compliance is imperative for their successful treatment. The ADAGIO (Adherence Assessment with Glivec: Indicators and Outcomes) study from 2008 prospectively examined 168 patients and their ability to remain compliant with imatinib therapy. The researchers found that only 14.2% of patients were fully compliant with imatinib over the first 90 days of therapy.[5] Treatment interruptions of over 30 days have been observed in up to 31% of patients taking imatinib.[6] Treatment interruption and/or non-compliance with CML results in sub-optimal treatment response, resistance, and treatment failure. Marin and others found that major molecular response was not observed in patients who were less than 90% compliant with the prescribed TKI, whereas 43% of the compliant cohort was able to attain MMR at 6 years. Additionally, treatment compliance was the only independent predictor for inability to achieve MMR.[7]

Treatment for tuberculosis is also fraught with challenges due to stigma, side effects, access to care, and patients' ability to take multiple drugs. The size of pills and frequency of administration are barriers to correct administration of anti-tuberculosis agents. The World Health Organization (WHO) recommended Directly Observed Therapy, and Short-course (DOTS) in 1995 to overcome challenges in treatment compliance for TB.[4] Since 1995, the WHO and the United Nations, along with many other non-profit organizations, have committed to treating this life-threatening disease. Worldwide, approximately 49 million people were treated, and up to 6 million lives were saved because of DOTS and the Stop TB Strategies.[8]

Treatment of these two conditions simultaneously results in a unique subset of challenges. Metabolism of a TKI may be profoundly affected by anti-tuberculosis medications. Dasatinib is primarily metabolized by the CYP3A4 isoenzyme of cytochrome P450.[9] Concomitant administration of rifampin, a potent cytochrome P450 inducer, results in an 80% reduction in plasma concentration of dasatinib,[10] hence, they must not be co-administered. On the other hand, there is less data regarding co-administration of isoniazid (INH) and dasatinib. Isoniazid is a CYP3A4 inhibitor; metabolism of dasatinib would be impaired in a patient also taking INH, resulting in higher than the intended levels of dasatinib.

We report a patient who was successfully treated for both CML and TB. Because of the high cost, our patient was not compliant with dasatinib, but successfully completed the anti-TB regimen because of DOTS. Her major molecular response was lost while off of TKI therapy, but was re-established once treatment was resumed, despite continued treatment with anti-TB medications. In conclusion, this case suggests that patients with CML and TB can safely and effectively undergo treatment with a tyrosine kinase inhibitor and a non-rifampin based anti-TB regimen. Extended use of a fluoroquinolone and INH does not interfere with the efficacy of dasatinib to effectively treat CML and attain MMR.

Conflict of Interest

No conflicts of interest.

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