

Correspondence

To the editor:

Successful treatment using omacetaxine for a patient with CML and BCR-ABL1 35INS

An alternatively spliced *BCR-ABL* mRNA transcript with a 35-bp insertion (35INS) was recently described among patients with chronic myelogenous leukemia (CML), and has been associated with in vitro resistance to tyrosine kinase inhibitors.¹ We now describe a patient with CML and 35INS who had clinical resistance to imatinib and dasatinib, but a complete cytogenetic response to omacetaxine (previously known as homoharringtonine).

The patient, a 19-year-old woman with CML in chronic phase, initially had a complete hematologic and partial cytogenetic response to imatinib (400 mg/d). After 6 months of imatinib, she became noncompliant and was lost to follow-up. She returned 3 months later with recurrent chronic-phase CML. She experienced a second hematologic response to imatinib, but did not achieve cytogenetic remission. After 4 months of this second course of imatinib, a significant increase in BCR-ABL transcripts was observed, and therapy was changed to dasatinib (100 mg/d). However, she experienced persistent headaches during the subsequent 2 months and demonstrated a persistent rise in white blood cell count, leading to discontinuation of dasatinib. Salvage therapy with interferon alpha (5 000 000 units/m² per day subcutaneously) and cytarabine (20 mg/m² daily, subcutaneously, 10 days/month) reduced her white blood cell count but did not cause a cytogenetic or molecular response.

No HLA-matched donor was identified among her 3 siblings or the National Marrow Donor Program registry. ABL kinase mutation analysis demonstrated the presence of a 35 base-pair insertion between exons 8 and 9.

Compassionate-use treatment with omacetaxine (1.25 mg/m² per dose subcutaneously twice daily × 14 days in each 28-day period) was approved by the Institutional Review Board of the Albert Einstein College of Medicine, and was started after informed consent was obtained. She experienced a complete cytogenetic response after 3 months of treatment. At the time of this writing, 2 months later, the patient remains in cytogenetic remission, on maintenance dosing of omacetaxine (1.25 mg/m² twice daily × 7 days in each 28-day period), with no nonhematologic toxicity. BCR-ABL transcripts, measured by quantitative reverse-transcription–polymerase chain reaction, have decreased to 1.75%.

CML is characterized by t(9;22)(q34;q11) translocation which leads to the production of the BCR-ABL fusion oncoprotein, which contains an activated tyrosine kinase domain.² Acquisition of point

mutations commonly leads to resistance to imatinib and second-generation tyrosine kinase inhibitors by altering binding of drug to the kinase domain. Recently, an alternatively spliced *BCR-ABL* mRNA transcript with a 35-bp insertion (35INS) between *ABL* kinase domain exons 8 and 9 was identified.¹ Although the clinical significance of this variant is not yet known, in vitro studies suggest that 35INS is associated with resistance to tyrosine kinase inhibitors, but sensitivity to aurora kinase inhibitors or omacetaxine.³

Omacetaxine, a plant alkaloid with antitumor activity, is associated with inhibition of global protein synthesis, promotion of cell differentiation, and induction of apoptosis via a caspase-3–dependent mechanism.^{4,5} To our knowledge, our patient is the first reported patient with CML and the 35INS to show a complete cytogenetic response to treatment with omacetaxine. A prospective clinical trial to examine the efficacy of this drug among CML patients with the 35INS BCR-ABL appears to be warranted.

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To the editor:

Smoking is associated with an increased risk of acute chest syndrome and pain among adults with sickle cell disease

Acute chest syndrome (ACS) is a leading cause of hospitalization and death for people with sickle cell disease (SCD).¹ Cigarette smoking has been inconsistently related to an increased risk of ACS in prior studies^{2,3} and may be one of the few

potentially modifiable risk factors for ACS. We tested the hypothesis that adults with SCD with exposure to tobacco smoke have a higher rate of ACS episodes compared with adults who are not exposed.

Table 1. Adjusted negative binomial regression models for the effect of different levels of smoke exposure on rate of acute chest syndrome (ACS) and pain episodes in adults with SCD

Variable	Model 1: Effect of active smoking on the rates of ACS and pain events compared with those with no smoke exposure		Model 2: Effect of passive smoking on the rates of ACS and pain events compared with those with no smoke exposure	
	RR (95% CI)	P	RR (95% CI)	P
ACS*				
Active smoking	2.61 (1.24-5.51)	.01		
Environmental tobacco smoke exposure only			2.62 (1.05-6.57)	.04
Pain†				
Active smoking	1.94 (1.04-3.62)	.04		
Environmental tobacco smoke exposure only			1.59 (0.74-3.43)	.24

ACS indicates acute chest syndrome; SCD, sickle cell disease; RR, relative risk; and CI, confidence interval.

*Multivariable models of ACS were adjusted for SCD phenotype (HbSS/HbSβthal° vs others), age, hemoglobin, white blood cell count, history of asthma, hydroxyurea use.^{3,7}

†Multivariable models of pain were adjusted for SCD phenotype, age, sex, hemoglobin, history of asthma, hydroxyurea use.⁷⁻⁸

We examined a cohort of adults with SCD who had received all of their SCD care at Washington University continuously since 2004, were only hospitalized at Barnes-Jewish Hospital or affiliated hospitals, and completed questionnaires about smoke exposure.⁴ Electronic medical records from January 1, 2004, to March 1, 2009, were reviewed for ACS and pain episodes using standardized data extraction forms. After examining clinic records and reviewing study participants with SCD clinical personnel, patients known to have been admitted to hospitals outside of the Barnes-Jewish Hospital system were excluded from analyses. Enrollment into this study began in August 2006 and questionnaires were completed at the time of study consent. This study was approved by the Human Research Protection Office at Washington University and informed consent was obtained from participants. ACS was defined as a new infiltrate in the context of a respiratory illness with or without fever.⁵ Pain episodes were defined as hospitalizations with a primary diagnosis of pain related to SCD.⁶ The relationships between smoke exposure and rates of ACS and pain were examined using multivariate negative binomial regression models.

Our cohort was composed of 106 adults with SCD (median age 32.5 years, range 18-72 years). The prevalence of smoke exposure was high, with 38 (36%) active smokers and 18 (17%) nonsmokers who reported environmental tobacco smoke (ETS) exposure. Among the smokers, all reported they started smoking before 2004 when morbidity data collection began. In separate multivariate models, active smoking and ETS exposure were each associated with more than twice the rate of ACS episodes compared with no smoke exposure. There was also a significant association between active smoking and pain rate in the multivariate model (Table 1).^{3,7-8} To determine whether there was a dose effect associated with cigarette consumption, we limited the multivariate analysis to smokers. There was no dose effect for number of cigarettes smoked per day and rate of ACS ($P = .816$) or pain episodes ($P = .903$).

We can only postulate about potential mechanisms for the association between smoking and SCD-related morbidity. First, data from the general population indicates that both active cigarette smoking⁹⁻¹¹ and ETS exposure¹² increase vascular inflammation, platelet aggregation, and expression of endothelial adhesion molecules, processes that would increase vaso-occlusion. Second, adults with SCD who smoke may be increasing their risk of community acquired pneumonia (CAP). In a prospective cohort study of 26 429 men from the Health Professionals Follow-Up Study and 78 062 women from the Nurses' Health Study II, current

smoking was associated with an increased risk of CAP in both men (odds ratio [OR] 1.46, 95% confidence interval [CI] 1.0-2.1) and women (OR 1.55, 95% CI 1.2-2.1).¹³ CAP is a known risk factor for ACS.³

The association between smoking and ACS in the present study was not shown in Cooperative Study of Sickle Cell Disease (CSSCD).³ In the CSSCD, however, patients with ETS exposure were not explicitly differentiated from active smokers or nonsmokers, potentially biasing results toward the null.

This study demonstrates a significant, clinically meaningful association between smoking and increased rate of ACS and pain events among adults with SCD. Although self-reported smoking status and use of a convenience clinic sample limit our results, these data provide additional rationale for SCD providers to emphasize smoking cessation to patients and their families. Lack of a dose effect for number of cigarettes smoked per day may be due to underreporting of amount smoked.¹⁴ Further systematic studies are needed to confirm these findings and define the mechanism by which cigarette smoking worsens SCD-related morbidity.

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