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 hematomic 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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References

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 studies2,3 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.
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