BRAF inhibition in hairy cell leukemia with low-dose vemurafenib.

Abstract:
The activating mutation of the BRAF serine/threonine protein kinase (BRAF V600E) is the key driver mutation in hairy cell leukemia (HCL), suggesting opportunities for therapeutic targeting. We analyzed the course of 21 HCL patients treated with vemurafenib outside of trials with individual dosing regimens (240-1920 mg/d; median treatment duration, 90 days). Vemurafenib treatment improved blood counts in all patients, with platelets, neutrophils, and hemoglobin recovering within 28, 43, and 55 days (median), respectively. Complete remission was achieved in 40% (6/15 of evaluable patients) and median event-free survival was 17 months. Response rate and kinetics of response were independent of vemurafenib dosing. Retreatment with vemurafenib led to similar response patterns (n = 6). Pharmacodynamic analysis of BRAF V600E downstream targets showed that vemurafenib (480 mg/d) completely abrogated extracellular signal-regulated kinase phosphorylation of hairy cells in vivo. Typical side effects also occurred at low dosing regimens. We observed
the development of acute myeloid lymphoma (AML) subtype M6 in 1 patient, and the course suggested disease acceleration triggered by vemurafenib. The phosphatidylinositol 3-kinase hotspot mutation (E545K) was identified in the AML clone, providing a potential novel mechanism for paradoxical BRAF activation. These data provide proof of dependence of HCL on active BRAF signaling. We provide evidence that antitumor and side effects are observed with 480 mg vemurafenib, suggesting that dosing regimens in BRAF-driven cancers could warrant reassessment in trials with implications for cost of cancer care.