the pathogenesis of HCL. Although the BRAFV600E mutation is clonally presented in almost 100% of classical HCL patients, it has not been identified in patients with other B-cell malignancies. In addition, 2 novel mutations were identified in BRAFV600E-negative cases of HCL. This understanding of the BRAFV600E mutation has provided a rationale for the diagnosis of HCL, with potential therapeutic implications. However, the BRAFV600E mutation is not detected in the HCL variant (HCL-v) and IGHV4-34 variants of HCL. Recently, vemurafenib, an ATP-competitive BRAF inhibitor, has been shown to have potent antitumor activity in BRAFV600E-mutated HCL patients.

Thus far, no other recurrently mutated genes coexisting with BRAFV600E mutations have been identified in patients with classical HCL. Dietrich et al report their results of whole-exome sequencing and targeted sequencing analysis in 3 HCL patients refractory to purine analog, who received vemurafenib. This part of the study was followed by testing of novel mutations in a larger cohort of 81 patients with classical BRAFV600E-mutated HCL, who were refractory to purine analog. The authors identify mutations in EZH2 and ARID1A and recurrent inactivating mutations of the cyclin cycle inhibitor CDKN1B, in addition to mutations in BRAFV600E. Until this study, CDKN1B mutations had never been investigated specifically in HCL. Deleterious CDKN1B mutations were identified in 13 of 81 (16%) analyzed patients by deep sequencing of CDKN1B. In addition, in 11 of those 13 patients, the CDKN1B mutation was clonal, implying a role of this mutation in the pathogenesis of HCL. The authors report that mutation in CDKN1B is the second most common mutation in HCL.

The CDKN1B gene encodes the cyclin-dependent kinase inhibitor protein p27, which belongs to the Cip/Kip class of cyclin-dependent kinase inhibitors and inactivates the cyclin E-CDK2 complex. This protein performs complex functions in cell cycle regulation and is a known tumor suppressor. The p27 protein can exert either stimulatory or inhibitory effects on cell proliferation, cell motility, or apoptosis. Moreover, the upregulation of p27 can participate in the resistance of tumor cells to anticancer treatment. At high levels, p27 binds to the cyclin E-CDK2 complex, inhibiting its activity and allowing cell cycle arrest. In contrast, lower levels of p27 protein stabilize cyclin D-CDK4/6 complexes and facilitate cell cycle progression.

Recent studies have shown that the CDKN1B gene may also play a role in the pathogenesis of other hematologic malignancies, including T-cell prolymphocytic leukemia (T-PLL), acute myeloid leukemia (AML), and lymphomas. An important role in the pathogenesis of T-PLL is played by CDKN1B haploinsufficiency. AML patients with low CDKN1B expression were found to demonstrate longer event-free survival than those with intermediate or high expression. In chronic lymphocytic leukemia, high levels of p27 are associated with rapid disease progression and poor outcome. However, CDKN1B mutations are very rare in these leukemias and other malignancies and do not coexist with BRAFV600E (see figure). Future studies should clarify whether the mutation of CDKN1B may contribute to the pathogenesis of HCL and what its impact on clinical outcome could be. In the highlighted study here, the CDKN1B mutation was found to have no impact on clinical characteristics or response to standard therapy with purine analog. However, further analysis of the signaling pathways related to this mutation may allow a clearer understanding of this finding and its possible application in clinical practice, both as a prognostic factor and a specific therapeutic target.

In conclusion, Dietrich et al demonstrate that CDKN1B is inactivated in 16% of patients with classical HCL and that it is the second most commonly mutated gene in HCL. These observations strongly suggest that CDKN1B plays a potential role in the biology and pathogenesis of HCL, particularly in neoplastic cell cycle deregulation and tumor suppression.

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MYELOID NEOPLASIA

Comment on Barete et al, page 1009

Cladribine for mastocytosis: benefits and risks

Cem Akin  HARVARD MEDICAL SCHOOL

In this issue of Blood, Barete et al report the safety and efficacy of cladribine in 68 adult patients with mastocytosis. Cladribine (2-chlorodeoxyadenosine) is a purine analog that causes apoptosis in cells after phosphorylation intracellularly
to 2-chlorodeoxyadenosine-5’-triphosphate, which incorporates to DNA and causes DNA strand breaks. It does not require active cell division for this effect and therefore is ideal for a disorder like mastocytosis in which neoplastic mast cells often do not show a high rate of mitosis except in the most advanced and rare forms of the disease. This property of cladribine is also responsible for its major toxicity because it causes T- and B-cell lymphopenia, immunosuppression, and opportunistic infections along with overall bone marrow suppression. There has been also some concern that it may be associated with secondary malignancies, although conclusive data are lacking about this point.

The effect of cladribine as a cytoreductive agent in advanced mastocytosis (aggressive systemic mastocytosis, mastocytosis with an associated hematologic non–mast-cell disorder, and mast-cell leukemia) has been well recognized. It is often advocated as the first line of therapy in these disorders. Cladribine causes apoptosis in mast cells independent of the presence of the common D816V KIT mutation (which confers resistance to imatinib) because its mechanism of action does not involve tyrosine kinase inhibition. Currently available tyrosine kinase inhibitors do not show significant cytoreductive responses in KIT D816V+ mastocytosis.

The most important decision in using cladribine for systemic mastocytosis lies in the determination of the risk-vs-benefit ratio. This decision is easy to reach in patients with advanced mastocytosis who have a shortened life expectancy. Patients with indolent mastocytosis, however, have a life expectancy comparable with that of the age-matched general population, with an overall low rate of progression to advanced disease (currently estimated to be ~3%). Therefore, the risk and benefit analysis in patients with indolent systemic mastocytosis (ISM) should consider not only the risk of progression into advanced disease but also the symptomatic status of the patient. Patients with mastocytosis often have symptoms of mast-cell mediator release including flushing, itching, abdominal cramps, nausea, vomiting, diarrhea, tachycardia, and hypotension, which may lead to syncopal or presyncopal episodes. Disabling fatigue and musculoskeletal pain are reported by some patients, although it is not clear whether these latter symptoms are directly related to mast-cell mediator release. Approximately 80% of patients with systemic mastocytosis have urticaria pigmentosa, a fixed hyperpigmented rash that involves the trunk and extremities. Because there is no curative treatment for mastocytosis, these symptoms are treated with ant mediator drugs such as H1 and H2 antihistamines, antileukotriene drugs, cromolyn, glucocorticoids, and epinephrine. Although most patients see at least a partial improvement with ant mediator therapy, some remain symptomatic and may require repeated emergency department evaluations for recurrent anaphylaxis-like episodes. This population may be candidates for cladribine therapy, after careful consideration and a full discussion with the patient of the risks and benefits of the drug. I would not recommend its administration to patients with purely cutaneous disease.

The current study by Barete et al included, in addition to 32 patients with advanced variants, 28 patients with ISM, 2 with smoldering systemic mastocytosis, and 6 with cutaneous mastocytosis, although one cannot rule out the presence of systemic mastocytosis in the latter 6 patients because it is very unusual to have disease limited to the skin in an adult population. Although it is the largest series reported thus far, the current study is not the first to report the use of cladribine in indolent or smoldering mastocytosis. The first report of cladribine in a patient with mastocytosis by Tefferi et al appears to be of a patient with ISM with frequent anaphylactic episodes that resolved after therapy. Klun-Nelemans et al reported a series of 10 patients, 3 of whom had indolent disease refractory to symptomatic treatment. Wimazal et al reported 2 patients with smoldering mastocytosis who had recurrent life-threatening anaphylaxis and saw a positive symptomatic response to cladribine. The Mayo Clinic reported 10 patients with ISM, with an overall response rate of 56% in evaluable patients. Interestingly, all published reports also confirm a significant reduction in the intensity of urticaria pigmentosa skin lesions.

The immunosuppressive and myelosuppressive effects of cladribine are of major concern. The current study reports that 47% of patients developed grade 3 or 4 neutropenia, and 82% had prolonged lymphopenia, including 1 patient with indolent disease who required stem cell transplantation because of persistent pancytopenia after cladribine. Twenty-two percent had infectious complications and 1 died of septic shock. There were 2 solid tumors observed during the observation period. None of the patients with ISM progressed to having aggressive mastocytosis.

The mechanism of action of cladribine in inducing symptomatic improvement in these patients remains to be elucidated. Although cladribine use is associated with a significant decrease in tryptase level and a reduction in bone marrow mast-cell infiltrates, it does not cause complete remission. Given the observation that mast-cell burden poorly correlates with mast-cell activation, there may be additional mechanisms through which cladribine may induce symptomatic improvement. Optimum dosing regimens, routes (IV, subcutaneous, or oral) and the value of combination therapies (eg, with tyrosine kinase inhibitors) need to be investigated in future clinical trials.

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