To the editor:

Lysine-specific demethylase 1 (LSD1) in hematopoietic and lymphoid neoplasms

Recently, inhibition of lysine-specific demethylase 1 (LSD1) has gained attention as a potential novel treatment in acute myeloid leukemia (AML). However, expression in other hematologic neoplasms has not been examined. LSD1 is a central epigenetic regulator of chromatin, acting in concert with many different activating and repressive histone-modifying complexes. It regulates self-renewal and differentiation in human embryonic stem cells and is overexpressed in a wide variety of human neoplasms. LSD1 depletion disrupts hematopoietic differentiation, and LSD1 has been shown to play a pivotal role in the maintenance of hematopoietic stem cells and differentiation of granulopoiesis, thrombopoiesis, and erythropoiesis. In murine leukemia models, targeting of LSD1 via tranylcypromine analogs abrogated oncogenic potential and induced differentiation of tumor cells. Inhibition of LSD1 was effective in non-acute promyelocytic leukemia AML.

To widen the range of hematologic and lymphatic malignancies that may be targeted by using LSD1 inhibitors, we examined the expression of LSD1 in normal, reactive, and neoplastic diseases in bone marrow trephine biopsies (n = 197) as well as lymphoid neoplasms in biopsies from lymphatic tissues (n = 354). Bone marrow from patients with a completely normal blood count (biopsy obtained for staging purpose) were mostly negative for LSD1 (1 [6.7%] of 15) (Table 1), whereas LSD1 was expressed in the majority of reactive bone marrow samples, especially in erythroid cells and megakaryopoiesis (18 [66.7%] of 27).

In myeloproliferative neoplasms, excluding chronic myelogenous leukemia, LSD1 was expressed in half the patients (26 [50.0%] of 52), mainly in megakaryocytes, in erythroid cells and, to a lesser degree, in early myeloid cells. In chronic myelogenous leukemia, LSD1 was expressed in one third of the patients (6 [31.6%] of 19), primarily in myeloid cells and megakaryocytes. Further, in myelodysplastic syndromes, more than half the patients (9 [56.3%] of 16) demonstrated nuclear expression in dysplastic megakaryocytes and early erythroid cells. Atypical myelocytic and monocytic cells as well as megakaryocytes showed LSD1 expression in chronic myelomonocytic leukemia (5 [50.0%] of 10). LSD1 was expressed frequently in a blast-specific nuclear pattern in primary and secondary AMLs (21 [46.7%] of 45). LSD1 expression in lymphoid malignancies was observed in 123 of 354 patients or 34.7% overall. Low-grade B-cell non-Hodgkin lymphomas (B-NHLs) expressed LSD1 less often (19 [12.9%] of 147) than did high-grade B-NHLs (52 [39.7%] of 131) (Pearson χ² test P < .001) (Table 1). Both, T-cell NHLs (14 [66.7%] of 21) and Hodgkin lymphomas (38 [69.1%] of 55) showed LSD1 expression more frequently than B-NHLs (71 [25.5%] of 278) (Pearson χ² test P < .001 for both).

On the basis of these results, we conclude that in addition to in AML, LSD1 is overexpressed in myeloproliferative neoplasms, chronic myelomonocytic leukemia, and myelodysplastic syndromes, possibly widening the spectrum of diseases amenable to LSD1 inhibitor therapy. Expression in reactive hematopoiesis needs to be considered when using LSD1 inhibitors to treat these diseases, consistent with concerns raised by other investigators. However, transient cytopenias may still be manageable because more established cytotoxic therapies also affect hematopoiesis.

Whether patients with the above-mentioned diseases would benefit from treatment with LSD1 inhibitors requires further investigation.

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

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References
Table 1. LSD1 expression in normal and reactive hematopoiesis and hematopoietic and lymphoid neoplasms

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<th>ICD-O-3</th>
<th>Intensity of expression</th>
<th>Mean age (y)</th>
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To determine LSD1 expression in hematopoiesis and hematopoietic neoplasms, bone marrow trephine biopsies were decalcified and immunostained by using a monoclonal anti-mouse antibody against LSD1 (1:500; Novus Biologicals, Littleton, CO). Intensity of expression was assessed as either none or background (negative) or moderate or strong (positive). Expression was positive in myeloproliferative neoplasms (MPNs), myelodysplastic syndrome (MDS), normal bone marrow, and reactive bone marrow if 1 to 3 lineages showed intensive expression, which was most often observed in the erythroid and megakaryocytic lineage. In acute leukemias, blasts only were scored. To determine LSD1 expression in lymphoid neoplasms, tissue microarrays of lymphoid tissues were immunostained with anti-mouse antibody against LSD1 (1:500; Novus Biologicals, Littleton, CO). Intensity of expression was assessed as either none or background (negative) or moderate or strong (positive). 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