

EZH2. Thus, Van der Meulen and colleagues hypothesized that UTX-deficient cells might be more sensitive to inhibitors of these methyltransferases. Indeed, the authors found that UTX knockdown rendered leukemic cells more sensitive to DZNep, a small molecule whose cellular effects include inhibition of EZH2.

Intriguingly, although UTX and EZH2 have antagonistic methylation activity at H3K27, both UTX and EZH2 function as tumor suppressors in T-ALL.^{1,4-6} One potential explanation for this apparent discrepancy is that UTX and EZH2 may have distinct transcriptional targets. Indeed, additional H3K27 “writer” methyltransferases and “eraser” demethylases exist, so that UTX and EZH2 need not necessarily function as an antagonistic pair for the maintenance of balanced H3K27 methylation at individual loci. In fact, recent work has shown that JMJD3 (also known as KDM6B), a UTX-related H3K27 demethylase, is bound by NOTCH1 and required for the maintenance of NOTCH1-induced T-ALL.⁴ By contrast, UTX does not bind NOTCH1 and suppresses NOTCH1-induced tumorigenesis.⁴ Thus, a speculative model to explain these observations is that EZH2 and JMJD3 may function as an antagonistic “writer-eraser” pair, with the UTX “eraser” being antagonistic to a different H3K27 methyltransferase. Such a model would mimic the antagonistic relationships that are conserved across substrates for some kinase-phosphatase pairs.⁷

The tumor suppressor function of UTX could also be mediated by functions independent of its ability to demethylate H3K27. Such possibilities include demethylation of lysine residues on nonhistone substrates or demethylase-independent functions. For example, UTX has been shown to interact with the switch/sucrose nonfermentable (SWI/SNF) chromatin-remodeling complex,⁸ a key tumor suppressor in diverse human cancers. Indeed, recent data have demonstrated that the tumor suppressor BCL11B, which is recurrently inactivated in human T-ALL, is a dedicated SWI/SNF subunit.^{9,10} Thus, UTX deficiency might represent an alternative mechanism for disabling the tumor suppressor function of SWI/SNF in T-ALL.

Unraveling the role of chromatin-modifying enzymes in T-ALL has important potential therapeutic implications. The overexpression of oncogenic transcription factors plays key

roles in T-ALL, yet transcription factors have proven to be largely intractable targets for drug development. However, transformation by oncogenic transcription factors is strongly influenced by the accessibility of their binding sites within DNA, which is highly regulated by chromatin-modifying enzymes such as UTX and EZH2. These enzymes are much more tractable therapeutic targets than transcription factors. Thus, unraveling the precise role of such chromatin-modifying enzymes in T-ALL pathobiology could reveal therapeutic strategies to specifically reverse oncogenic gene expression programs. Indeed, the work of Van der Meulen et al¹ and of Ntziachristos et al⁴ provides a compelling rationale for testing inhibitors of 2 such enzymes, EZH2 and JMJD3, in molecularly defined subsets of T-ALL.

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

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CLINICAL TRIALS & OBSERVATIONS

Comment on Hughes et al, page 71

Limited effect of chemotherapy in cutaneous lymphoma

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In this issue of *Blood*, Hughes et al report the lack of durable disease control with chemotherapy for mycosis fungoides (MF) and Sézary syndrome (SS).¹

Mycosis fungoides is the most common type of cutaneous T-cell lymphoma (CTCL), characterized by the slowly progressive forming of patches to more infiltrated plaques that eventually become tumors. In a minority of patients, lymph nodes and visceral organs may become involved in the later stages of the disease. Sézary syndrome is a leukemic variant of CTCL that presents with erythroderma, generalized lymphadenopathy, and the presence of neoplastic T cells (Sézary cells) in the skin, lymph nodes, and peripheral blood.² Early stages of MF are treated with skin-directed therapies (SDTs), such as topical corticosteroids, psoralen

plus UVA radiation (PUVA), narrowband UVB phototherapy, or local radiotherapy.^{3,4} The best treatment for patients whose disease can no longer be controlled by these SDTs is controversial. For many years, such patients have been treated with single-agent or multiagent chemotherapy, but the results are generally disappointing. In recent years, a large number of nonchemotherapeutic systemic therapies have become available, such as α -interferon, bexarotene, histone deacetylase inhibitors (HDACi), monoclonal antibodies, fusion toxins, and extracorporeal photopheresis. Because there are no curative options apart from allogeneic

hematopoietic stem cell transplantation (AlloSCT), which is only applicable in a minority of patients, the clinical benefit of these systemic treatments should be carefully balanced against their toxicity and side effects. However, the decision of whether systemic chemotherapy or one of these nonchemotherapeutic systemic agents should be used in these patients is difficult to make, because comparative studies have not been done. The study by Hughes et al fills this gap by comparing retrospectively the efficacy of many chemotherapeutic and nonchemotherapeutic systemic agents in a group of 198 patients with MF and SS.

A particular strength of the study is the selection of time to next treatment (TTNT) as the primary end point. In current trials, the extent of skin disease is evaluated using detailed scoring systems such as the modified severity-weighted assessment tool (mSWAT).⁵ However, this measurement tool was only recently adopted and its use is limited in a retrospective study. The TTNT used by the authors provides genuine insight into the durability of responses as assessed in daily practice, and it provides a clinically relevant measure of effectiveness.

Previous studies showed that aggressive systemic chemotherapy in the early stages of MF is associated with considerable morbidity but does not result in increased survival.⁶ In the present study, it was found that in patients with only patches and plaques (stages IA-IB), and also in patients with only skin tumors but no extracutaneous disease (stage IIB), α -interferon gave significantly longer TTNT than HDACi and chemotherapy. In addition, in patients with advanced stages of disease with lymph node and blood involvement (stages IVA-IVB), treatment with α -interferon and HDACi resulted in longer TTNT than did systemic chemotherapy. Also when stratified by skin (T) score, α -interferon provided significantly better disease control than chemotherapy for T1 (patches and plaques <10% body surface area), T2 (patches and plaques >10% body surface area), and T4 (erythrodermic disease). Finally, extracorporeal photopheresis was especially effective in erythrodermic (T4) patients.

The relatively favorable clinical results of immunomodulatory agents (PUVA, α -interferon, HDACi, extracorporeal photopheresis) illustrate that immunomodulation can be an effective strategy in controlling disease and are in line with the presence of an active immune response against tumor cells in MF and

SS. Indeed, previous studies have shown an active cytotoxic immune response in MF lesions, and rapid progression of disease has been observed in patients who were mistakenly treated with immunosuppressive agents.⁷

In a small number of patients, AlloSCT was performed, resulting in excellent disease control. Recent retrospective studies evaluated AlloSCT results in MF/SS patients and reported an overall survival at 2 years ranging from 45% to 76%, and of those patients, 50% to 80% remained disease free.⁸⁻¹⁰ With further development of safe and effective AlloSCT protocols, it is likely that more MF/SS patients will be selected for this treatment, which makes it even more pertinent to avoid cumulative toxicity from relatively ineffective chemotherapy early in the disease course that may later hinder AlloSCT.

The results from this study confirm that current chemotherapy regimens have modest efficacy in MF/SS, and they argue against the routine use of systemic chemotherapy in patients before immunomodulatory therapies have been used.¹ Based on these results, future prospective studies using more sophisticated clinical staging systems such as mSWAT will be instrumental in further quantifying the therapeutic effectiveness of different treatment regimens. Ultimately, recommendations from these studies should be incorporated into guidelines that can help treating physicians select optimal treatment for patients whose disease can no longer be controlled with SDT.

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

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Comment on Kolstad et al, page 82

Dendritic cells and lymphoma cells: come together right now

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In this issue of *Blood*, Kolstad et al report an elegantly designed and well-implemented study showing that intratumoral injection of ex vivo-produced immature dendritic cells (DCs), granulocyte macrophage colony-stimulating