fates, thereby creating a larger pool of precursor cells in which acquired genetic and/or epigenetic lesions induce frank malignancy.

Given the prominent role PTEN has in expanding the numbers of self-renewing HSCs, it will be important to assess if and how PTEN regulates proliferation in committed, lineage-restricted progenitor cells and leukemia. For example, it is possible that *PTEN* loss both expands lymphoid progenitor cells and increases the overall frequency of self-renewing leukemia propagating cells. Moreover, the downstream pathways mediated by the PTEN/PI3K/AKT signaling axis to ultimately expand progenitor pools, induce malignancy, and maintain leukemic cells has not been fully defined, especially in T-ALL. The PTEN/PI3K/AKT pathway has many downstream effectors including MYC stability to enhance proliferation, activation of the mammalian target of rapamycin (mTOR) pathway to induce dexamethasone resistance in lymphoid malignancies, and suppressed apoptosis through regulation of BAD and NF-κb.[8] Dissecting which of these and other downstream pathways regulate lineage-restricted progenitor cell expansion and leukemic cell maintenance will likely be important for identifying novel therapies for the treatment of a wide range of hematopoietic malignancies. Finally, it will be important to identify the hematopoietic cell stages at which *Pten*-deficient progenitor cells are arrested (see figure), defining whether the PTEN/PI3K/AKT axis exerts differential effects on multipotent or unipotent progenitor cells. The work from Choorapoikayil et al provides critical insights and a relevant zebrafish model to begin to address these important biological and clinical questions.

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● ● ● CLINICAL TRIALS & OBSERVATIONS

Comment on Rosenberg et al, page 177

Hairy cell: young living longer but not cured

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In this issue of *Blood*, Rosenberg et al provide a detailed retrospective description of the long-term outcome of young patients with a diagnosis of hairy cell leukemia treated with cladribine.[1]

The introduction of the purine nucleoside analogs about a quarter of a century ago dramatically changed the natural history of this once-untreatable chronic leukemia.[2,3] The importance of the current study is that it provides data on a large number of patients under the age of 40 years treated in a fairly uniform fashion at a single institution coupled with careful long-term follow-up. Although the purine analogs can control the disease by achieving complete and durable remissions, the patients are not yet cured. This retrospective study by Rosenberg and colleagues focuses on the clinical characteristics and course of those patients most likely to face the consequences of relapse. Although the statement that the current treatments may provide an opportunity for young patients with this disease to experience "survivals approximating that of healthy individuals,"[1] they will also have to confront the probability of multiple relapses.

The complete remission rate enjoyed by the younger patients was 88% with a median duration of response at 57 months, yet the observation is that the majority of patients will eventually relapse. There is a tremendous range of response duration, from 7 to 246 months. When the therapy was delivered more than 2 decades earlier, immunophenotyping was not routinely included in response determinations. In current therapeutic protocols, immunohistochemical and immunophenotypic analysis are capable of defining minimal residual disease following therapy.

Increasing interest in defining molecular and genotypic biomarkers promises to identify the prognostic subsets with more accuracy. There are new discoveries recently reported regarding the significance of identifying the BRAFV600E mutation in the majority of patients with the classic form of this disease, which has both diagnostic and therapeutic potential for advancement in management.[4] Although the clinical entity of the hairy cell leukemia variant is now distinctly separated from classic hairy cell leukemia by World Health Organization revised criteria, there is increasing evidence that patients with classic hairy cell leukemia who have certain biomarkers (eg, unmutated immunoglobulin gene rearrangement, use of the immunoglobulin gene IGHV4-34, negative marker for the BRAFV600E mutation, or p53 deficit) are likely to have a worse prognosis.[5,6] Other studies have suggested that the extent of minimal residual disease posttherapy may ultimately prove to have prognostic importance, yet some of the patients with minimal residual disease have long-lasting periods not requiring therapy. Although the current study provides substantial evidence for the positive impact of

therapy with cladribine, the variability in time to relapse illustrates the necessity to clearly identify those patients potentially requiring more therapy than a single course of this highly effective agent.

This paper also shows the difference in response duration and survival between those achieving a complete remission vs a partial remission following a single course of therapy. These observations highlight the potential advantage of characterizing the quality of bone marrow response achieved following cladribine therapy. As this report shows, patients who relapse have a high salvage rate for second remission. The durability of subsequent remissions declines with repeated therapies. Although current salvage therapy with cladribine is highly effective in achieving a second remission following relapse, optimizing therapy for young patients with this disease in the future will require identification of those at highest risk for early relapse. These individuals may benefit from novel therapy either with combined chemoimmunotherapy or the evaluation of newer agents (eg, specific immunotoxin conjugates, inhibitors of BRAFV600E, or experimental agents directed at targets uniquely expressed in the malignant cells).[7,8] The introduction of these novel therapies for high-risk younger patients should be conducted in a carefully designed clinical trial rather than being randomly explored in clinical practice.

Despite a commonly held belief that this disease has been "conquered," there are many unanswered questions deserving of further study.[9] This disease affords opportunities to explore the biology and importance of minimal residual disease. The bone marrow microenvironment is under investigation in other forms of chronic leukemia as a potential source impacting the ultimate survival of leukemia cells. The substantial variability of response duration in hairy cell leukemia suggests that genomic profiling of the leukemic cells and further exploration of the microenvironment in the bone marrow and spleen may provide a better understanding of relapse and potential improvement in outcome.[10]

This study has tremendous value in providing the outcome of a closely followed cohort of younger patients treated in a center with extensive experience with this agent. Although initial studies with cladribine excluded patients with active infection, there is a need to define how best to approach patients with an active infection who require therapy for their leukemia. Continued surveillance of secondary malignancies will also be important. Considering the prevalence of BRAFV600E mutations in malignant melanoma and thyroid cancer, the finding of this same signature mutation in this rare leukemia would warrant additional epidemiologic studies to understand the relationship of these findings. Exploring novel therapies based upon prognostic subsets, defining optimal management of the infectious and immune-based complications inherent in this disease, and attempting to provide guidance for these complicated patients will require interinstitutional collaborative studies. While the group at Scripps has accumulated enormous experience with this rare disease, this report represents the culmination of 20+ years of follow-up on 88 young patients. Recently, efforts have been made to establish a network of international institutions with special interest in this disease. The Hairy Cell Leukemia Foundation will strive to address questions that will ultimately expedite the development of new therapeutic strategies. Rosenberg and colleagues have made great progress toward improving the quality and quantity of life for patients with this disease. The dramatic responses observed with cladribine inspire the collective institutions dedicated to improving the outcome of these patients by continuing work to ultimately achieve a more durable remission for these young patients seeking a cure rather than control.

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● ● ● HEMATOPOIESIS & STEM CELLS

Comment on Speth et al, page 203

Opening the door for HIF1α tuning

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In this issue of *Blood*, Speth et al identify the beneficial effects of a pharmacologic stabilizer of hypoxia-inducible factor-1α (HIF1α) for the efficient trafficking of hematopoietic stem and progenitor cells (HSPCs) to the bone marrow niche.[1]

Bone marrow transplantation is an effective therapy for various hematologic diseases. However, insufficient numbers of transplanted hematopoietic stem cells (HSCs) can result in failure of engraftment. Thus, it has long been a dream to robustly enhance