several important cell-cycle regulators including Cdkn1a and Id1. Consistent with this finding, Id1 deficiency recapitulates many of the HSC abnormalities found in Scl−/− mice.12,13 These results uncover a new and subtle effect of Scl gene dosage/expression on regulating the cell-cycle transitions required for stress conditions that demand high levels of self-renewal, such as limiting dilution transplantation experiments in serial recipients. Given the importance of maintaining HSC reserve for conditions of proliferative demand, these results provide a significant new insight into the role of Scl/Tal1 in hematopoiesis and illustrate the importance of stress models for teasing out elusive phenotypes. It is also noteworthy that relatively modest changes in Scl gene dosage and expression were sufficient for these effects, an observation that is consistent with other known haploinsufficient phenotypes in HSC biology.14,15

**Conflict-of-interest disclosure:** The author declares no competing financial interests.

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**Clinical Trials**

Comment on Horning et al, page 775

**PET positive, PET negative, or PET peeve?**

**Jonathan W. Friedberg**

**University of Rochester**

In this issue of *Blood*, Horning and colleagues report that there was disagreement by 3 nuclear medicine experts on interpretation of FDG-PET images obtained in the context of a clinical trial in aggressive non–Hodgkin lymphoma 32% of the time.1 These results emphasize the need for standardized criteria to interpret interim PET scans in lymphoma and should cause physicians to question the practice of changing therapy based on PET imaging outside the context of a trial.

PET imaging is a functional imaging technique that uses a glucose analog (2-fluoro-2-deoxy-D-glucose [FDG]) radiolabeled with the positron emitter fluorine-18 to evaluate glycolytic activity, which is increased in most histologies of lymphoma.2,3 Several studies have suggested a role for FDG-PET in the diagnosis and follow-up of patients with lymphoma, and PET is now recommended as part of routine staging and assessment of response in curable lymphomas—particularly diffuse large B-cell lymphoma and Hodgkin lymphoma.4

More recently, there has been significant interest in performing “interim” PET scans after 2 to 3 cycles of chemotherapy as an early biomarker of resistant disease. A frequently cited trial extolling the benefits of early interim PET enrolled 260 patients with de novo Hodgkin lymphoma and performed a PET scan after 2 cycles of standard ABVD (combination of doxorubicin/bleomycin/vinblastine/ dacarbazine) chemotherapy.1 No treatment change was permitted on the basis of the interim PET scan. Two-year progression-free survival for patients with positive interim PET (n = 50) was only 12% and for patients with negative interim PET exceeded 95%. Somewhat lost in these exciting results are details regarding interpretation of the PET scans. Two international expert readers were required to reach consensus for each positive scan. Moreover, lesions with “minimal residual uptake,” arbitrarily defined as a standardized uptake value between 2 and 3.5, were considered to be negative. These criteria have never been evaluated prospectively. Despite these limitations, as a result of this study, cooperative groups in both Europe and the United States are evaluating treatment algorithms that change therapy based on an interim positive PET scan. Many physicians have already adopted this practice. Indeed, a very common question in our consultation clinic is “what to do with an interim positive PET scan?”

For more than a decade, it has been clear that understanding of physiologic uptake and artifacts associated with FDG is critical to accurate interpretation of PET scans.1 False-positive scans can result from brown fat, rebound thymic uptake, and increased diffuse bone marrow and muscle uptake at the completion of therapy, which do not represent refractory disease. Indeed, preliminary results of a trial that incorporated biopsies of PET-positive sites following R-CHOP therapy (rituximab plus cyclophosphamide/doxorubicin vincristine/prednisone) for diffuse large B-cell lymphoma revealed that only a minority of the biopsies (4 of 36) were positive for lymphoma.2,3

However, for the clinician, binary criteria (positive or negative) are easiest to interpret. Two years ago, consensus criteria were developed for interpreting scans after completion of chemotherapy. Mediastinal blood pool activity was recommended as the reference background activity to define PET positivity in lymphoma, and specific recommendations were provided for interpretation of extranodal sites.4 These international criteria were not
used for any studies incorporating interim PET imaging.

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Jonathan W. Friedberg