However, the cutoff values mentioned in this publication must be assessed with caution. These values are derived from a single-institution and a retrospective dataset. The authors emphasized that validation of these findings, with PET-CT scans obtained using a standardized approach, is essential.

In recent years, the guidelines for standardization of PET-CT scanning for oncologic studies have been performed by hematologists, nuclear medicine physicians, and clinical physicists from Hemato-Oncology Foundation for Adults in the Netherlands,[5] the European Association of Nuclear Medicine, and the Society of Nuclear Medicine.[6,7] These guidelines were designed to achieve SUV consistency for multicenter settings, that assist physicians in performing, interpreting, and reporting the results of PET-CT. For example, the interval between injection and start of scanning (60 vs 90 minutes) will influence the quantification of FDG uptake and thereby also the MTV measurement. Therefore, image quantification needs to be standardized also regarding the reconstruction methods and settings used.

Another important issue is the contouring of MTV. There is no universal consensus on how to define and assess MTV.[8] Several absolute and relative thresholds have been suggested, and none of these has proven consistently superior to the others, as Akhtari and colleagues correctly state. To illustrate these differences, 1 PET-CT scan has been analyzed with different commonly used MTV contouring methods (cutoff SUV 2.5; SUV 4.0; SUV 41%max; SUV A50%), resulting in a range of MTVs from 253 mL to 2082 mL (see figure).

Akhtari and colleagues have performed an accurate and significant analysis of baseline PET-CT characteristics in early-stage HL. Moreover, they have raised the critical issues of the definition and importance of bulky disease. However, an individual patient data meta-analysis based on results of prospective clinical trials in HL is needed to solve the above-mentioned issues that still exist with regard to the contouring of MTV. For implementation in daily practice and for use in clinical studies, a semiautomated, reliable, and easy-to-use contouring method is needed.

We conclude that, in HL, the MTV as baseline characteristic seems of additive value in risk stratification. However, standardization of PET-CT scanning has to be implemented, and definition of MTV measurement procedures has to be settled before MTV can be used for clinical decision-making.

For daily practice, the interim-PET in correlation with baseline PET is important because chemosensitivity is mainly reflected by interim-PET assessment. Recent publications in early- and advanced-stage HL have emphasized the predictive value of interim-PET using visual assessment.[9,10] The relationship between baseline MTV and interim-PET assessment, visually or by using semiquantitative parameters, is intriguing and the subject of ongoing studies. It is most likely that, in the near future, baseline characteristics as well as interim-PET–adapted treatment strategies will enhance individually designed and tailored therapy, supporting maximal efficacy and minimal toxicity!

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

REFERENCES

1. Akhtari M, Milgrom SA, Pinnix CC, et al. Reclassifying patients with early-stage Hodgkin lymphoma based on functional radiographic markers at presentation. *Blood*. 2018;131(1):84-94.
2. Specht L, Nordentoft AM, Cold S, et al. Tumor burden as the most prognostic factor in early stage Hodgkin's disease. Relations to other prognostic factors and implications for choice of treatment. *Cancer*. 1988;61(8):1719-1727.
3. Cheson BD, Fisher RI, Barrington SF, et al; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014; 32(27):3059-3068.
4. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol*. 2014;32(27): 3048-3058.
5. Boellaard R, Oyen WJ, Hoekstra CJ, et al. The Netherlands protocol for standardisation and quantification of FDG whole body PET studies in multi-centre trials. *Eur J Nucl Med Mol Imaging*. 2008;35(12):2320-2333.
6. Boellaard R, Delgado-Bolton R, Oyen WJ, et al; European Association of Nuclear Medicine (EANM). FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur J Nucl Med Mol Imaging*. 2015;42(2): 328-354.
7. Aide N, Lasnon C, Veit-Haibach P, Sera T, Sattler B, Boellaard R. EANM/EARL harmonization strategies in PET quantification: from daily practice to multicentre oncological studies. *Eur J Nucl Med Mol Imaging*. 2017; 44(suppl 1):17-31.
8. Burggraaff CN, Kassner I, Rahman F, et al. Interobserver reproducibility of semi-automated assessment of metabolic tumour volume (MTV) in DLBCL patients. In: Proceedings from the International Workshop on PET in Lymphoma; 19 September 2016; Menton, France. Abstract G2.
9. André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: final results of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol*. 2017;35(16):1786-1794.
10. Borchmann P, Goergen H, Kobe C, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *Lancet*. 2017;20(6736): 32134-32137.

DOI 10.1182/blood-2017-11-812958

HEMATOPOIESIS AND STEM CELLS

Comment on El Ashkar et al, page 95

LEDGF: a leukemia-specific target

Thomas A. Milne | University of Oxford

In this issue of *Blood*, El Ashkar et al[1] reveal that the lens epithelium-derived growth factor (LEDGF) protein is a key therapeutic target by showing that it is essential for leukemia, but not normal hematopoiesis. Such context-dependent information is important for the development of new targeted therapies.

The goal of precision medicine is to be able to specifically target the disease state in individual patients with minimal toxic side effects. A detailed understanding of the molecular basis of a disease is an important aspect of achieving this goal. Part of this is

understanding the context-dependent activity of specific targets, the most important comparison being normal cells vs the disease state. It is challenging to answer these questions precisely in humans; thus, animal models provide a robust system for answering clearly defined questions about context specific function.

LEDGF (also known as PC4 and SFRS1-interacting protein 1 or PSIP1) was originally identified as the p75/p52 component of PC4, a transcriptional coactivator.[2] It is also famous for being the integration target of HIV.[3] Importantly, LEDGF also has a crucial role in the development of a rare but aggressive subset of leukemias caused by mutations in the mixed lineage leukemia (*MLL*) gene.[4] The most common *MLL* mutations fuse *MLL* in frame with a wide range of different partner genes creating novel fusion proteins (MLL-FPs).[5] MLL-FPs cause leukemia by binding to gene targets and causing their inappropriate upregulation. LEDGF was originally proposed to be crucial for anchoring MLL-FP proteins to their specific gene targets,[4] but more recent work has suggested that LEDGF may instead have a different role in controlling the assembly of other transcription components at gene targets.[6]

Because LEDGF has a clear importance in leukemia progression, several attempts have been made to inhibit the LEDGF/MLL-FP interaction.[4,7-9] One key piece of information that has been missing until now is whether a robust inhibitor would disrupt normal blood development. In other words, is there a therapeutic window where one could effectively target LEDGF without causing more general toxic effects in the blood system?

Using a hematopoietic-specific knockout system, El Ashkar et al completely removed LEDGF from normal blood cells in the mouse. They found that, although there were some measurable defects in hematopoiesis, overall the mice were healthy and still retained a fully functional hematopoietic system. Conversely, cells that were deleted for LEDGF were completely resistant to developing MLL-FP–driven leukemia, although other oncogenes were still able to transform these cells.[1] Together, these data suggest that it is now worth developing more robust inhibitors to LEDGF because it appears to be possible to disrupt MLL-FP leukemogenesis without affecting normal blood cell development.

Although this work focuses on a specific target protein that is only important in a rare subset of leukemias, it represents an important proof of principle. This study provides an important example of the robust information needed to justify a more comprehensive drug development program. It also highlights that there may be very few general targets that will work across multiple different cancers. If this is the case, individual patients may themselves represent their own rare kind of cancer, potentially requiring similar specific information on an increasingly wide range of different candidate therapeutic targets.

Conflict-of-interest disclosure: T.A.M. is a founding shareholder of OxStem Oncology, a subsidiary company of OxStem Ltd (2016). ■

REFERENCES

1. El Ashkar S, Schwaller J, Pieters T, et al. LEDGF/p75 is dispensable for hematopoiesis but essential for MLL-rearranged leukemogenesis. *Blood*. 2018;131(1):95-107.
2. Ge H, Si Y, Roeder RG. Isolation of cDNAs encoding novel transcription coactivators p52 and p75 reveals an alternate regulatory mechanism of transcriptional activation. *EMBO J*. 1998;17(22):6723-6729.
3. Llano M, Saenz DT, Meehan A, et al. An essential role for LEDGF/p75 in HIV integration. *Science*. 2006;314(5798):461-464.
4. Yokoyama A, Cleary ML. Menin critically links MLL proteins with LEDGF on cancer-associated target genes. *Cancer Cell*. 2008;14(1):36-46.
5. Meyer C, Hofmann J, Burmeister T, et al. The MLL recombinome of acute leukemias in 2013. *Leukemia*. 2013;27(11):2165-2176.
6. Zhu L, Li Q, Wong SH, et al. ASH1L links histone H3 lysine 36 dimethylation to MLL leukemia. *Cancer Discov*. 2016;6(7):770-783.
7. Méreau H, De Rijck J, Cermáková K, et al. Impairing MLL-fusion gene-mediated transformation by dissecting critical interactions with the lens epithelium-derived growth factor (LEDGF/p75). *Leukemia*. 2013;27(6):1245-1253.
8. Murai MJ, Pollock J, He S, et al. The same site on the integrase-binding domain of lens epithelium-derived growth factor is a therapeutic target for MLL leukemia and HIV. *Blood*. 2014;124(25):3730-3737.
9. Cermáková K, Tesina P, Demeulemeester J, et al. Validation and structural characterization of the LEDGF/p75-MLL interface as a new target for the treatment of MLL-dependent leukemia. *Cancer Res*. 2014;74(18):5139-5151.

DOI 10.1182/blood-2017-11-815449

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Dossa et al, page 108

Off-the-shelf TCR for graft-versus-leukemia without GVHD

Frederick L. Locke and Claudio Anasetti | Moffitt Cancer Center and Research Institute

In this issue of *Blood*, Dossa et al report the engineering of T-cell receptor (TCR) transgenic T cells against the human minor histocompatibility antigen HA-1 for the prevention or treatment of leukemia relapse after allogeneic stem cell transplantation.[1]

With the recent US Food and Drug Administration approval of chimeric antigen receptor (CAR) T cells for immunotherapy of CD19$^+$ B-cell leukemia and lymphoma,[2,3] why pursue such a complex approach for the treatment of hematological malignancies?

The development of adoptive cell therapies for myeloid diseases has not advanced to the same degree as anti-CD19 CAR T-cell therapies. Extensive studies using genomics and proteomics suggest that an ideal surface target may not exist in acute myeloid leukemias (AMLs).[4] Myeloid lineage–specific molecules are shared with hematopoietic stem cells, a clear limitation for the development of CAR T cells directed against nonpolymorphic cell surface receptors: