Assuringly, recent data suggest that the incidence after low-dose TBI is not higher than in patients conditioned with chemotherapy-only regimens.[7]

What else is required? We need data on larger numbers of patients, preferentially treated in a multicenter setting and followed for longer. Such a study should include more older patients who have a worse prognosis of aplastic anemia. Also, we do not have results from prospective randomized trials comparing upfront BMT from HLA-haploidentical donors with results of IST, possibly combined with eltrombopag,[8] particularly in children (effect of TBI on growth?). On the other hand, IST still comes with the risk of clonal evolution.[9] A multicenter study in pediatric patients comparing BMT (from unrelated donors) with IST is currently ongoing (NCT05600426). Although the trial does not enroll haploidentical donors, additional data relevant for BMT decision-making should emerge. Finally, should a regimen as used for HLA-haploidentical transplants in patients with aplastic anemia also be used for patients receiving HLA-identical transplants? Preliminary data suggest that the incorporation of posttransplant Cy is of similar benefit.[10]

Conflicts-of-interest: The author declares no competing financial interests. ■

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LYMPHOID NEOPLASIA

Comment on Eertink et al, page 3055

A man's best friend is his PET

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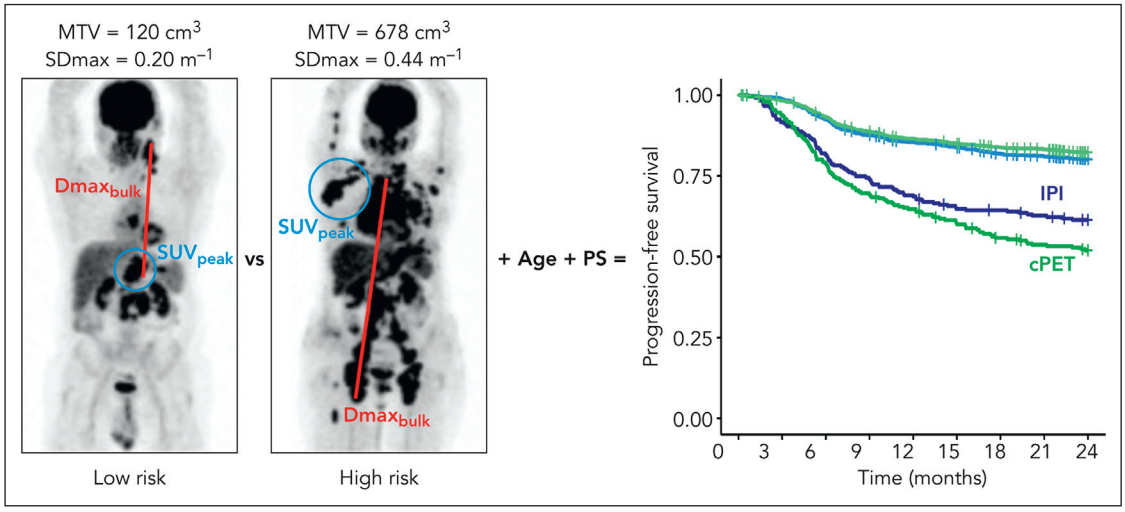
In this issue of *Blood*, Eertink et al[1] validate that a new radiomics-based prognostic classification outperforms the traditional International Prognostic Index (IPI) in identifying patients with diffuse large B-cell lymphoma (DLBCL) who are at high risk for treatment failure.

DLBCL is the most common lymphoma histology. Although this disorder is an aggressive one, 50% to 70% of patients are cured with initial standard chemoimmunotherapy. However, currently no method is routinely available to identify, prior to therapy, those patients who are unlikely to benefit and should therefore be considered for an alternative treatment. The unfortunate consequence is that all patients with DLBCL are currently treated the same, regardless of differences in their predictable prognosis. At presentation, patients with DLBCL are given an anatomic stage, per the 4-stage Ann Arbor (AA) system that dates back to 1971. Next, they are assigned to a prognostic group according to the somewhat archaic, 30-year-old IPI, which uses simple clinical and laboratory features, including age, performance status, serum lactate dehydrogenase, number of extranodal sites, and AA stage. Unfortunately, neither AA stage nor IPI provides adequate information for therapeutic guidance. Thus, the range of treatment results has remained relatively stagnant.

Over the past 2 decades, the precision of staging and restaging has improved greatly, owing largely to the availability of 2′-fluorodeoxyglucose positron emission tomography–computed tomography (FDG-PET-CT) scanning. PET-CT is more sensitive and specific than simple CT scans, and it helps distinguish viable tumor from fibrous tissue.[2] In several histologies, PET-CT has eliminated the need for subjecting patients to the dreaded bone marrow biopsy. Improvements in equipment and better standardization of interpretation with the 5-point Deauville score have further enhanced the usefulness of PET-CT. Such advances justified, in part, the revised staging and response criteria used to classify nodal lymphomas—the widely used Lugano classification of 2014.[3]

Recent enhancements in metabolic imaging have further improved the ability to predict, pretreatment, which patients are likely to benefit from therapy. Numerous studies have demonstrated that the quantification of metabolic tumor volume (MTV) derived from the PET-CT scan is highly correlated with patient outcome in DLBCL[4] as well as other lymphoma histologies. Radiomics, or quantitative FDG-PET features, examines other characteristics of the lymphoma phenotype, including the peak standardized uptake value, the



In the clinical PET (cPET) radiomics model, the combination of metabolic tumor volume (MTV), peak standardized uptake value (SUV_{peak}), maximum distance between the largest lesion and its most distant lesion ($Dmax_{bulk}$), patient age, and performance status (PS) outperformed the standard International Prognostic Index (IPI) in identifying the group of patients with diffuse large B-cell lymphoma (DLBCL) with the most unfavorable prognosis. SDmax, maximum standard deviation. The left side of the figure is adapted from an image supplied by M. Meignan with permission. The right side is modified from Figure 3 in the article by Eertink et al that begins on page 3055. Professional illustration by Patrick Lane, ScEYEnce Studios.

tumor shape and heterogeneity, and the greatest distance between the largest and most distant lesions.[5] These, and many others, alone and in combinations, appear to outperform the IPI alone. Several groups have now developed prognostic systems combining one or more of these metabolic features with standard clinical features, producing promising results.[6]

In the current article, Eertink et al report the results of a validation study of the clinical PET scoring system, originally tested in the HOVON-84 study, now including a larger number of patients from 6 different clinical trials. Their system included MTV, the value for the greatest distance between the largest and most distant lesions, the peak standardized uptake value, and the simple clinical factors of patient age and World Health Organization performance status. The results achieved with clinical PET were superior to those achieved with the IPI, and perhaps other published radiomics-based systems, in distinguishing patients unlikely to do well with respect to 2-year progression-free survival, thereby offering a potential advance in the management of DLBCL patients (see figure). Unfortunately, although clinical PET improves the ability to identify high-risk patients by almost 10%, compared with the IPI, more than half of the group with the poorest prognosis (51.9%) were still free of progression or death at 2 years. Whereas the clinical PET data are quite encouraging, no group can be readily identified for whom the treatment is sufficiently unlikely to be favorable and should be altered de novo. Studies currently examining molecular genetic signatures[7] and circulating tumor DNA[8] provide further hope for identifying clinically meaningful patient subsets.

In June 2023, at the International Conference on Malignant Lymphoma (ICML)-17, in Lugano, Switzerland, a workshop will be convened to determine whether revisions of the Lugano classification for patient evaluation, staging, and response criteria for lymphomas are warranted.[3] The large number of issues to be discussed include the following: Can we simplify, standardize, and improve upon the current anatomic staging system, incorporating prognostic factors, while making it more useful for a wide audience of physicians? Should MTV supplant CT as a measurement of tumor bulk? Are the newer technologies, such as MTV, radiomics, and circulating tumor DNA, ready for "prime time"? What is the role of these technologies in assessing minimal residual disease? The exciting preliminary data relating to use of these advances will make it hard to resist moving ahead with vigor to adopt them. However, we need to temper our enthusiasm a bit; for a new staging or prognostic classification to be useful, all the components must be not only validated but also widely available.

The holy grail for DLBCL is a risk-adapted approach in which the next generation of prognostic and predictive factors will help guide us in reducing treatment, and thus cost and toxicities, for the groups of patients for whom these methods are likely to be favorable, while altering our approach to improve outcome for those less likely to benefit from standard of care. Whereas clinical PET is clearly a major step in the proper direction toward individualization of therapy, there is still room for an upgrade. Incorporation of additional prognostic factors in the future should further enhance its performance. But, improved therapies and predictive biomarkers are needed to achieve true success. "Success is a science: if you have the conditions, you get the result" (Oscar Wilde).

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Comment on Jibril et al, page 3065

Targeting mtDAMPed macrophages for MM therapy

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In this issue of *Blood*, Jibril et al[1] demonstrate that multiple myeloma (MM) cells release cell-free, circulating mitochondrial DNA (mtDNA), a form of mitochondrial damage associated molecular patterns (mtDAMPs), which activate macrophages via the guanosine monophosphate-adenosine monophosphate synthase (cGAS)/guanosine monophosphate-adenosine monophosphate (cGAMP)/stimulating interferon gene (STING)-signaling pathway, thereby promoting the retention of tumor cells within the bone marrow (BM) microenvironment and disease progression in murine models.

Despite unprecedented therapeutic advances during the last 2 decades, MM remains as an incurable disease. Therefore, there is still an urgent need for more efficacious, well-tolerated drugs.[2] It is well established that the BM tumor microenvironment (TME) plays a fundamental role in MM pathogenesis. The multifaceted role of macrophages in this disease has only recently been elucidated. Tumor-associated macrophages (TAMs), predominantly immunosuppressive CD206$^+$ M2 macrophages, are a fundamental component of the MM TME. They support MM cell homing to and colonization of the BM. In addition, they play a critical role in MM cell proliferation, survival, chemo-protection, drug resistance, as well as in direct immune suppression. Unlike macrophages derived from healthy donors, macrophages derived from the BM of patients with MM lack the ability to present antigens, to engulf tumor cells, and to stimulate adaptive immune responses.[3] In addition, they downregulate expression of crucial cytotoxic T-cell factors. Attacking vulnerabilities of TAMs in the MM TME therefore represents a promising therapeutic avenue to further improve patient outcome.

Mitochondria are the "engines" of the cell but also are fundamental for amino acid metabolism, protein synthesis, gluconeogenesis, fatty acid oxidation, generation of reactive oxygen species (ROS), calcium homeostasis, and the initiation of apoptosis. Tumor cells are characterized by altered bioenergetic processes, such as an increased glucose metabolism, altered calcium regulation, altered ROS production, and inhibition of apoptotic processes. These changes may result, at least in part, from free cytoplasmic mtDNA, which characteristically contains unmethylated CpG nucleotide motifs and belongs to the group of mtDAMPs of the innate immune system.[4]

Our understanding of the cyclic cGAS/cGAMP/STING signaling pathway, which is responsible for danger sensing by the innate immune system, has grown dramatically. Upon mtDNA binding, the DNA sensor cGAS catalyzes the production of cGAMP, which in turn binds to and activates the adapter protein STING. Activated STING then migrates from the endoplasmic reticulum to the Golgi apparatus and activates downstream interferon regulatory transcription factor (IRF)-3 and NF-κB signaling cascades, thus inducing the expression of type I interferon and other inflammatory factors (eg, interleukin-6, tumor necrosis factor). cGAS and STING agonists may represent a promising strategy for cancer immunotherapy. Indeed, preclinical data demonstrated that STING agonists significantly promote antitumor immunity in acute myeloid leukemia, breast cancer, and small cell lung cancer.[5] In the context of macrophages, cGAS agonists have been proposed to trigger antitumor effects via repolarization of tumor-promoting M2-type TAMs into M1-type inflammatory macrophages, leading to enhancement of major histocompatibility complex class molecules or costimulatory molecules that drive recruitment, maturation, activation, and differentiation of CD4$^+$ and CD8$^+$ T cells to produce intense antitumor responses.[6] Based on these findings, there are ongoing preclinical and early clinical studies evaluating the ability of STING agonists in tumors cells or tumor-infiltrating immune cells (including dendritic cells) to elicit immunostimulatory effects, alone or in combination with a conventional chemo- and immunotherapeutics or radiotherapy. However, STING activation may also contribute to cancer initiation and progression, for example, by activating cancer-associated inflammation; by hampering the immune response through infiltration of the TME with immunosuppressive cells such as T-regulatory cells (Tregs), myeloid-derived suppressor cells, or TAMs; or by upregulating the expression of immune checkpoints, programmed death-ligand 1 (PD-L1) on tumor cells and programmed cell death protein 1 (PD-1) on