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FDG/PET in CLL today

Stefano Molica

In this issue of *Blood*, Falchi et al present their experience with 2-deoxy-2-[18F]fluoroglucose/positron emission tomography (FDG/PET) in the management of patients with chronic lymphocytic leukemia (CLL) or Richter syndrome (RS) over a 10-year period at a referral center. The results of this study shed light on the potential role of FDG/PET in CLL.1

Although not recommended on a routine basis, FDG/PET has been useful to suspect the transformation of CLL into RS and to select the optimal site for performing a diagnostic biopsy.2-4 The MD Anderson Cancer Center (MDACC) group previously reported on PET/CT scans in 37 CLL patients under the clinical suspicion of RS transformation, showing that cases with histologically proven RS had a mean maximum standardized uptake value (SUVmax) roughly 4 times higher than patients with no histological transformation.2 Furthermore, an SUVmax ≥5 was found to be a consistent threshold affording high sensitivity and specificity for diagnosing RS. Since then, other studies have confirmed SUVmax ≥5 on PET/CT as a reliable cutoff to identify CLL patients with clinically suspected RS.2,4 Because the diagnosis of RS requires histological...
confirmation, PET/CT is useful to identify sites in which a tissue biopsy is more likely to be diagnostically informative.4,5

The article by Falchi et al1 in this issue updates the MDACC experience and reports data on the largest cohort thus far published of CLL or RS patients (n = 332) with FDG/PET evaluation and concurrent available lymph node histology. This single-institution study aims to correlate FDG/PET with histology, clinical features, and survival. Although an SUVmax ≥ 5 is validated as a meaningful cutoff to identify the optimal site to detect RS, an SUVmax ≥ 10 had the best discriminatory power to predict survival. Not unexpectedly, patients with higher SUVmax were more likely to present with poor prognostic features such as 17p deletion or ZAP-70 positivity. Moreover, in multivariate analysis, SUVmax ≥ 10 was independently associated with a shorter overall survival.1

Worthy of note is the attempt to correlate FDG/PET findings with lymph node histology. To that purpose, cases were classified as having: histologically indolent CLL; histologically aggressive CLL (HA-CLL) (see figure); or RS.1 Not surprising, but still important, information is that fine-needle aspiration proved to be inadequate for detecting disease transformation. Interestingly, patients with HA-CLL and RS shared similar FDG/PET patterns and traits of disease aggressiveness (eg, constitutional symptoms, high lactate dehydrogenase [LDH] values) but patients with HA-CLL had a better survival (median: 17.6 vs 7.7 months). These observations are in keeping with those previously reported by Montserrat’s group,6 which identified patients with aggressive disease and a survival intermediate between CLL and RS under the term of “accelerated CLL.”

It is worth mentioning, however, that criteria for defining CLL histological subgroups have not been agreed upon nor validated. CLL guidelines, for example, only recognize RS as a form of CLL transformation.7,8 On the other hand, in the study under consideration, an SUVmax ≥ 10 but not histology was retained as a prognostic variable in controlled survival analysis, which is an interesting finding warranting additional investigation. That in CLL, because it occurs in other indolent lymphoid malignancies,9 there is a continuous spectrum of lesions from typical to fully transformed cases should not be surprising and fits with our current understanding of CLL pathogenesis.10 With this in mind, the different FDG/PET patterns observed in CLL are most likely a mere reflection of different, but unfrozen, phases of CLL biology.

Where do we stand today in using FDG/PET to benefit CLL patients? FDG/PET is important for detecting disease transformation, a not infrequent phenomenon that in the case of RS can be estimated to occur in around 10% of patients. Disease transformation, which is frequently overlooked, has an extremely poor prognosis and requires aggressive therapy.3,9 There are some clinical hints to suspect disease transformation, including the development of general symptoms, enlarging lymphadenopathy, and increasing LDH. A positive FDG/PET not only supports the possibility of transformation but points to the site where a biopsy is more likely to be informative. On the other hand, the available studies do not justify using FDG/PET routinely in the prognostic evaluation or response to therapy assessment in patients with untransformed CLL.

The MDACC group study sets the stage for other prospective studies to further elucidate the role of FDG/PET in the management of CLL. Meanwhile, outside of clinical trials, FDG/PET has an important role in supporting the possibility of disease transformation and guiding tissue biopsy.

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Comment on Treon et al, page 2791

Waldenström macroglobulinemia: genetics dictates clinical course

Georg Lenz1  CHARITÉ - UNIVERSITÄTSMEEDIZIN BERLIN

In this issue of Blood, Treon and colleagues provide strong evidence that mutations in MYD88 and CXCR4 dictate clinical presentation and survival in Waldenström macroglobulinemia (WM).1

WM is a rare malignancy of immunoglobulin M–secreting B cells.2 Recent work identified recurrent somatically acquired activating mutations in MYD88 as well as in CXCR4 in WM patient samples.3,4 In more than 90% of WM patient samples, the MYD88 L265P mutation is detectable. This aberration, which is also found in other
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