Waldenström macroglobulinemia: genetics dictates clinical course

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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 $\geq$5 is validated as a meaningful cutoff to identify the optimal site to detect RS, an SUVmax $\geq$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 $\geq$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, 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 $\geq$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 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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REFERENCES
lymphoma subtypes such as the activated B cell–like subtype of diffuse large B-cell lymphoma (ABC DLBCL) or mucosa-associated lymphoid tissue lymphoma, leads to constitutive activation of the oncogenic nuclear factor-κB signaling pathway. 5,7 CXCR4 is a chemokine receptor that promotes survival of WM cells. 4 Different mutations affecting the C terminus of CXCR4 can be identified in roughly 30% of WM patients. 4 Although these analyses provided important insights into the molecular pathogenesis of WM, it remained unclear if these genetic aberrations impact clinical presentation or survival of affected patients.

In this issue, Treon et al investigate the clinical implications of MYD88 and CXCR4 mutations in WM. 1 Virtually all patients harboring mutations in CXCR4 also exhibited mutated MYD88. Patient samples harboring CXCR4 mutations were further distinguished based on the mutation pattern (nonsense vs frameshift mutations). Interestingly, the mutation status of CXCR4 and MYD88 was associated with significant differences in clinical presentation and outcome (see figure). 1 Patients with mutated MYD88 and CXCR4 nonsense mutations exhibited bone marrow infiltration significantly more frequently, had higher serum immunoglobulin M levels, and presented with symptomatic disease, including hyperviscosity, syndrome more frequently. In contrast, patients with mutated MYD88 and CXCR4 frameshift or nonsense mutations presented less frequently with adenopathy. Finally, patients that were wild type for both MYD88 and CXCR4 were characterized by adverse survival compared with patients with mutated MYD88 alone or patients that harbored both mutations. Taken together, these results suggest that the MYD88 and CXCR4 mutation status determines clinical presentation and outcome of patients diagnosed with WM (see figure). 1

From a clinical standpoint, the results by Treon et al can potentially be highly relevant for WM treatment. A better understanding which oncogenic pathways are activated and used in WM is a prerequisite for the optimal utilization of novel therapeutic agents. To this end, the determination of the MYD88 and CXCR4 mutation status might help us identify novel subgroups of WM that differ with respect to clinical presentation and prognosis. Additionally, these subgroups might benefit differentially to novel therapeutic strategies. Bruton’s tyrosine kinase, which interacts with MYD88, is a promising target for the treatment of WM, and encouraging results were obtained by using the Bruton’s tyrosine kinase inhibitor ibrutinib in relapsed and refractory WM. 8 Similarly, interleukin–1 receptor–associated kinase inhibitors that are being developed for clinical use hold promise for the treatment of WM because MYD88 coordinates the assembly of a signaling complex consisting of different members of the interleukin–1 receptor–associated kinase family. 5,6 Finally, the use of CXCR4 inhibitors such as plerixafor might be promising in WM patients with mutated CXCR4. Importantly, large and well-designed clinical trials with accompanying scientific programs are required to investigate if specific subtypes of WM respond preferentially to novel compounds. This approach will pave the way to more specific and less toxic treatment regimens for patients with WM.

**REFERENCES**


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**MYELOID NEOPLASIA**

Comment on Goodwin et al, page 2838

### Hallway gossip between Ras and PI3K pathways

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In this issue of *Blood*, Goodwin et al investigate the pathogenesis of juvenile myelomonocytic leukemia (JMML), demonstrating that mutant Shp2 induces granulocyte macrophage–colony-stimulating factor (GM-CSF) hypersensitivity and that the p110δ subunit of phosphatidylinositol 3-kinase (PI3K) further promotes this dysregulation.1

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