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LYMPHOID NEOPLASIA

Comment on Puig et al, page 2432

It's in your (peripheral) blood

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In this issue of *Blood*, Puig et al[1] compared immunoprecipitation mass-spectrometry (QIP-MS, now EXENT) of serum and next-generation flow cytometry (NGF) of the bone marrow for the assessment of measurable residual disease (MRD) in transplant-eligible patients with newly diagnosed multiple myeloma (MM). Analyzing serial, paired peripheral blood and bone marrow samples from patients treated in the phase 3 GEM2012MENOS65 and GEM2014MAIN clinical studies, the authors provided important pieces of information about the complementarity between peripheral blood and bone marrow MRD assessments and the potential application of MS as a tool for disease monitoring and its prognostic power.

MM provides a unique opportunity to measure disease burden in the peripheral blood due to the presence of a circulating monoclonal protein produced by malignant plasma cells. However, current treatment strategies for MM, including quadruplet induction therapy, autologous stem cell transplant, and T-cell-redirecting therapies, are stretching the standard response assessment to its limits, as 60% to 80% of patients treated upfront achieve bone marrow MRD negativity by NGF or next-generation sequencing (NGS) at a sensitivity of 10^{-5}.[2,3]

MS is a highly sensitive technique for the detection of a monoclonal protein for patients with plasma cell dyscrasias. For this purpose, 2 different approaches have been tested: a clonotypic peptide (eg, M-Insight, Sebia) and the intact light chain approach (eg, QIP-MS/EXENT, Thermo Fisher).

Puig et al confirmed the higher sensitivity of QIP-MS as compared with standard serum immunofixation and electrophoresis (sIFE), as QIP-MS was able to detect a monoclonal protein in up to 15% of $sIFE^-$ patients and identify, among $sIFE^-$ patients, 2 groups of patients ($QIP\text{-}MS^+$ vs $QIP\text{-}MS^-$) with a distinct progression-free survival (PFS). Response criteria based on sIFE are no longer a reliable instrument to measure residual disease and inform patient prognosis using the current treatment strategies.[4] Bone marrow MRD assessment via NGS or NGF at a sensitivity of $\geq 10^{-5}$ has become the gold standard for evaluation of these patients. The recently published meta-analysis EVIDENCE demonstrated that bone marrow MRD status correlates with both PFS and overall survival of patients with MM,[5] thus supporting the Food and Drug Administration endorsement of MRD as a surrogate end point in clinical trials for accelerated drug approval. Not only has MRD been adopted as primary end point in a growing number of studies, but it is also being investigated as a decision-making tool for MRD-driven treatment strategies in clinical trials.[6]

Bone marrow MRD assessment has some important limitations. The most obvious one is its invasive nature, which impacts patients' compliance and quality of life. Bone marrow MRD is assessed at a single, random site, which does not take into account the spatial heterogeneity of MM.[7] This leads to false-negative results in cases of patchy infiltration, extramedullary disease, or focal skeletal lesions, as showed in a recent report in which 62% of patients with a relapse within 6 months after a confirmation of bone marrow MRD negativity had focal or extramedullary relapse.[8]

Peripheral blood techniques measuring circulating tumor DNA, cell-free DNA, plasma cells, or monoclonal proteins hold the promise to measure whole-body residual disease in a noninvasive fashion. Among these, MS has currently demonstrated the highest sensitivity and specificity, representing an ideal candidate for longitudinally monitoring for patients with MM. In their article, Puig et al provided important findings about the role of QIP-MS in MM. A promising overall agreement between QIP-MS and NGF was observed (75%-85%); however, such agreement decreased significantly when NGF, at a sensitivity between ≥10-6 and >10-5, was used as a reference, with 60.4% of QIP-MS negative patients resulted as NGF positive. Conversely, $QIP\text{-}MS^+$ but NGS^- cases were reported in up to 16% of patients in the study published by Kubicki et al,[9] a phenomenon due to several factors, such as the prolonged half-life of the monoclonal protein or the presence of extramedullary disease. In addition, despite QIP-MS and NGF both being able to stratify patients with a different PFS, NGF did retain a stronger prognostic value than MS. Taken together, these results suggest that today bone marrow MRD assessment still remains the gold standard for prognostication and treatment decisions, but MS may play a complementary role, as suggested by the reduced risk of

progression or death for double negative patients (MS^- and NGF^-), as opposed to patients only negative with either one. Another important, yet open, question concerns the impact of MS in the assessment of extramedullary disease and focal lesions, currently performed by whole-body imaging. Indeed, replacing imaging with a peripheral blood technique such as MS would represent an important step forward for patients with MM, and future studies investigating all 3 assessments (peripheral blood, bone marrow, and imaging) are warranted.

Puig et al also provided initial insights on the timing of MS testing. The concordance between QIP-MS and NGF was lowest at early time points (eg, post-transplant, 77%) and peaked at later time points (eg, during maintenance, 85%), in line with data published by Kubicki et al where the agreement between QIP-MS and NGS increased from 61% at screening to 74% after 18 cycles of treatment.[9] During the maintenance phase, a resurgence of bone marrow MRD predated conventionally defined relapse by almost 2 years, and the reappearance of a monoclonal protein detected by QIP-MS predated relapse by less than 1 year. This reflects the higher tumor burden needed by MS to turn positive in comparison with NGF. However, this shorter time span may provide a more clinically meaningful piece of information to physicians about the need to change or reinitiate treatment to prevent myeloma-related organ damage without the need of serial bone marrow assessments.

Trials investigating bone marrow MRD surveillance and treatment at MRD resurgence vs conventional relapse are ongoing (eg, REMNANT, NCT04513639), and results generated should be complemented by MS data as well.

Conflict-of-interest disclosure: M.D. is on the advisory board of Adaptive Biotechnologies. R.M. declares no competing financial interests. ■

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MYELOID NEOPLASIA

Comment on Kemps et al, page 2439

XG family: does age trump genetics?

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Xanth- (derived from the word *xanthos*: "blond" or "yellow" in Greek) is a colorful prefix used in several cutaneous histiocytoses predominantly involved by lipid-laden macrophages: xanthoma, xanthogranuloma (XG), and xanthelasma. In this issue of *Blood*, Kemps et al[1] describe the clinicopathologic as well as molecular findings of 16 Dutch children with juvenile XG (JXG) involving extracutaneous soft tissues.

They found variable clinical courses and treatment requirements ranging from the frequently indolent cases managed with observation (some spontaneously regressed) or local resection to the rarely aggressive phenotypes requiring chemotherapy or targeted treatment. This was despite the uniform findings of genetic alterations implicated in histiocytoses including recurrent *clathrin heavy chain* (*CLTC*)–*spleen tyrosine kinase* (*SYK*) fusions or *colony stimulating factor-1 receptor* (*CSF1R*) mutations in most of their patients. Interestingly, in the 5 patients with adult XG (AXG) that they used for comparison, only 1 was found to have a mutation. Although the natural history and the molecular findings of JXG have been previously described, the novelty of this study lies in the knowledge we gained from this meticulous case series, which combined the 2 pieces of information. In JXG, the genotype does not predict the phenotype.

The XG family includes JXG, AXG, and Erdheim-Chester disease (ECD), all characterized on tissue biopsy by abnormal accumulation of histiocytes with macrophage lineage differentiation. As these entities may present identically under the microscope, they have historically been distinguished by age and anatomic distribution. When frequent $BRAF^{V600E}$ mutation was identified in ECD, there was hope that genetic alterations would allow distinction between the systemic form of XG (ECD) and localized, self-limited forms (JXG/AXG). Indeed, the $BRAF^{V600E}$ mutation present in about half of ECD cases is nearly absent in JXG/AXG, found only rarely in central nervous system lesions. However, subsequent identification of other MAPK