

Splenic marginal zone lymphoma is an uncommon B-cell malignancy representing ~8% of all non-Hodgkin lymphomas.³ This disease commonly arises in the context of autoimmune processes or chronic infectious diseases. Previous sequencing studies have identified recurrent mutations in key pathways in this disease, notably NOTCH2 mutations in approximately one-quarter of patients. Furthermore, loss of chromosome 7q31-32 is also frequently seen in marginal zone lymphoma.^{4,5} Although many patients have a good prognosis, the outcome of this disease can vary, with some patients having a more aggressive disease course or disease transforming to a more aggressive phenotype. Arribas et al, by performing integrated genome-wide DNA-promoter methylation profiling and comparing this with gene-expression profiling, identified a cluster of patients with high promoter methylation who had a very poor outcome compared with others who had a much lower methylation profile. The prognostic relevance of this profile was tested in a discovery set and subsequently validated in an independent cohort of patients. These findings provide an opportunity for patients with marginal zone lymphoma who have a poor prognosis to be prospectively identified based on their methylation profile.

DNA methylation is an epigenetic mechanism that has been implicated in the pathogenesis of chronic inflammatory diseases as well as malignancies, by regulating the differentiation, apoptosis, proliferation, and activation of different cell types.^{6,7} This is achieved through alteration of gene expression and regulation of cellular phenotype. The work by Arribas et al identifies methylation of 3 genes—*KLF4*, *CACNB2*, and *HTRAI*—as most important in defining the high-methylation cohort that is associated with a poor outcome. By integrating the methylation data with paired-gene-expression profiling data, they show an inverse correlation between methylation status and expression levels of these and other genes. They also show, using a functional network analysis, that methylation changes have a direct effect on transcription levels of a variety of key genes in the pathogenesis of marginal zone lymphoma. These include genes with significant roles in the fate and differentiation of cells, in cell communication

and signal transduction, and in regulation of apoptosis.

These different methylation profiles in splenic marginal zone lymphoma present a further opportunity to treat patients in the high-methylation cohort with demethylating agents such as decitabine. In this study, the authors found that the use of decitabine could reverse the methylation profile in both cell lines and primary patient specimens. Decitabine has been approved for use in the treatment of patients with myelodysplastic syndromes, including previously treated and untreated, de novo, and secondary myelodysplastic syndrome.⁸ Decitabine has been used to treat patients with lymphoma and chronic lymphocytic leukemia but has shown only modest clinical benefit.⁹ The use of decitabine in patients with splenic marginal zone lymphoma, specifically those with a high methylation profile, may be an opportunity to treat a group of patients who have a poor outcome with standard treatment and yet may be more likely to respond to this agent. The rational use of hypomethylating agents in a cohort of marginal zone lymphoma patients who are most likely to benefit is a potential future treatment approach.

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● ● ● MYELOID NEOPLASIA

Comment on Savona et al, page 1857

Speaking a common language in MDS/MPNs

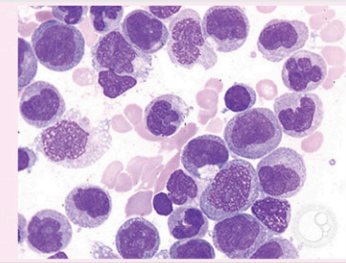
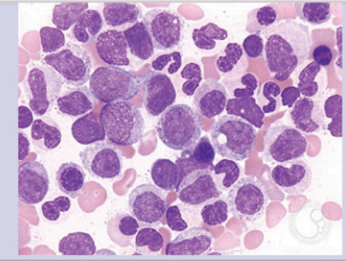
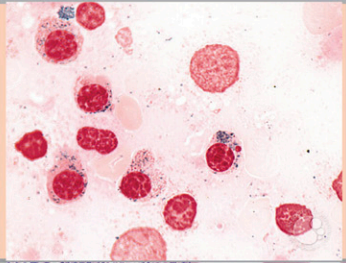
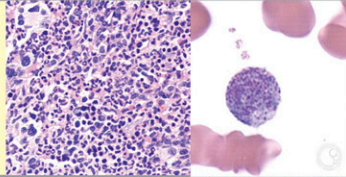
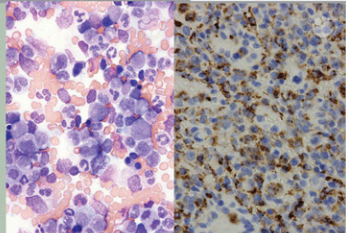
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In this issue of *Blood*, Savona and an international consortium of clinical investigators propose uniform response criteria for treatment trials enrolling adult patients with myelodysplastic/myeloproliferative neoplasms (MDS/MPNs).¹ Such a proposal is needed because new drugs are finally being tested in these rare “overlap” syndromes that have both dysplastic and proliferative pathological features, and neither the International Working Group (IWG) response criteria for myelodysplastic syndromes² nor the IWG Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) response criteria for myelofibrosis³ or for other myeloproliferative neoplasms fit such patients well.

MDS/MPNs are clinically heterogeneous and biologically poorly understood, although some pathophysiological insights

have begun to emerge from high-throughput genetic analyses and murine models.⁴ Four somewhat distinct clinicopathological

Key features of myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

<p>Chronic myelomonocytic leukemia (CMML)</p> <p>Most commonly diagnosed MDS/MPN; splenomegaly is frequent</p> <p>Defined by:</p> <ul style="list-style-type: none"> Persistent peripheral blood monocytosis ($>1 \times 10^9/L$ and $\geq 10\%$ of leukocytes) No <i>BCR-ABL1</i> fusion or <i>PDGFRA/PDGFRB</i> rearrangement $<20\%$ myeloblasts + monoblasts/promonocytes in blood and marrow Dysplasia in one or more myeloid lineages (or a clonal cytogenetic marker, or monocytosis x 3 months and other causes ruled out) <p>Deregulated GM-CSF and Ras signaling common</p> <p>Frequently associated mutations: <i>ASXL1</i>, <i>SRSF2</i>, <i>TET2</i>, <i>KRAS/NRAS</i>, <i>CBL</i></p>	
<p>Atypical chronic myeloid leukemia (aCML)</p> <p>Can be mistaken for CML, but dysplasia is more prominent</p> <p>Defined by:</p> <ul style="list-style-type: none"> Persistent leukocytosis ($\geq 13 \times 10^9/L$) Immature circulating neutrophil precursors ($\geq 10\%$ of leukocytes) Marked dysgranulopoiesis and hypercellular marrow $<20\%$ blasts in blood and marrow No <i>BCR-ABL1</i> fusion or <i>PDGFRA/PDGFRB</i> rearrangement Absent/minimal monocytosis ($<1 \times 10^9/L$, $<10\%$ of leukocytes) and basophilia (usually $<2\%$) <p>Associated mutations: <i>SETBP1</i>, <i>CSF3R</i> in some cases</p>	
<p>Refractory anemia with ring sideroblasts and thrombocytosis (RARS-T)</p> <p>Considered a provisional entity and subset of MDS/MPN-U in WHO 2008, but a real disorder</p> <p>Defined by:</p> <ul style="list-style-type: none"> Diagnostic features of RARS (anemia, $\geq 15\%$ ring sideroblasts, erythroid dysplasia) Persistent unexplained elevation in platelet count $>450 \times 10^9/L$ Other causes of thrombocytosis must be ruled out Megakaryocyte hyperplasia similar to that seen in essential thrombocythemia, but dissimilar to myelofibrosis $<5\%$ marrow blasts <p>Frequently has splicing mutations including <i>SF3B1</i>, and proliferative driver mutations (<i>JAK2</i>, <i>MPL</i>, or rarely <i>CALR</i>)</p>	
<p>Myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U)</p> <p>Diverse group of disorders with both MDS and MPN features that do not fit anywhere else</p> <p>Defined by:</p> <ul style="list-style-type: none"> No history of MDS or MPN and no recent therapy that might alter morphology No <i>BCR-ABL1</i> fusion or <i>PDGFRA/PDGFRB</i> rearrangement or isolated <i>del(5q)</i> or <i>chr. 3q21q26</i> rearrangement De novo disease that does not meet criteria for CMML, aCML or other WHO-defined disorders 	
<p>Juvenile myelomonocytic leukemia (JMML)</p> <p>Rare, aggressive pediatric neoplasm that usually presents before age 5; more common in boys</p> <p>Defined by:</p> <ul style="list-style-type: none"> Persistent peripheral blood monocytosis ($>1 \times 10^9/L$) No <i>BCR-ABL1</i> $<20\%$ myeloblasts + monoblasts/promonocytes in blood or marrow Minor criteria (at least 2 must be present): elevated Hb F, WBC $>10 \times 10^9/L$, GM-CSF hypersensitivity, leukoerythroblastic blood smear, clonal cytogenetic abnormalities (esp. monosomy 7) <p>Frequently associated with mutations of <i>PTPN11</i>, <i>NF1</i> (germline), Ras pathway members</p>	

WHO (2008) classification of MDS/MPNs: disease definitions and key molecular features. Chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), MDS/MPN-U, and left juvenile myelomonocytic leukemia (JMML) micrographs are Wright-Giemsa stained marrow aspirate. Right JMML micrograph is a CD68 immunostain highlighting neoplastic marrow monocytes, and refractory anemia with ring sideroblasts and thrombocytosis (RARS-T) image is a Prussian blue reaction demonstrating numerous ring sideroblasts. Microscopy conditions are described at <http://imagebank.hematology.org>. GM-CSF, granulocyte-macrophage colony stimulating factor; Hb F, fetal hemoglobin; MPN-U, unclassifiable MDS/MPN; WBC, white blood count; WHO, World Health Organization. Image source: ASH Image Bank (© American Society of Hematology); images (top to bottom) 2149, 2224, 2627, 4031, 2119, 1095, and 1098.

syndromes (see figure) are currently recognized by the World Health Organization (WHO)⁵: CMML (the most common syndrome in the group), JMML (an aggressive pediatric disease), aCML, and RARS-T (currently a “provisional” entity that will lose its provisional nature in the next WHO classification iteration). Rare patients who exhibit both cellular

dysplasia and myeloproliferative features but do not meet criteria for any of the specific syndromes are considered to have unclassifiable MDS/MPN, a diverse group with a highly variable clinical course.⁶

For the most part, because patients with MDS/MPNs other than JMML tend to be elderly, and outcomes with allogeneic

hematopoietic stem cell transplant in this group of neoplasms are notoriously poor, patients diagnosed with MDS/MPNs are treated primarily with palliative, supportive measures. Extramedullary hematopoiesis, leukocytosis, and thrombocytosis in MDS/MPNs are often approached with hydroxyurea or other cytoreductive agents, whereas hematopoietic growth factors,

androgens, corticosteroids, and other drugs are commonly employed as adjuncts to transfusions to ameliorate cytopenias. Occasionally, a hypomethylating agent such as azacitidine or an immunomodulatory drug such as lenalidomide can induce simultaneous improvement in both dysplastic and proliferative disease features, but such doubly good outcomes are infrequent, and disease-associated symptoms may persist even when blood counts improve.

Patients with MDS/MPNs rarely have specific molecular abnormalities targetable with currently available agents, which highlights the potential for improved approaches to these disorders in the near future. For instance, the recent finding of recurrent CSF3R mutations in aCML⁷ has prompted the use of dasatinib or ruxolitinib, depending on the specific CSF3R domain mutated; in our practice at Dana-Farber Cancer Institute, a number of patients with aCML have experienced favorable responses to these drugs. Because of the critical role of GM-CSF dysregulation and downstream JAK-STAT signaling in CMML biology, antibodies against GM-CSF and inhibitors of JAK2, including ruxolitinib, are currently being evaluated clinically in CMML.⁸ RARS-T is commonly associated with both spliceosome mutations, especially SF3B1, as well as mutations associated with cytokine signaling and myeloproliferation (eg, JAK2, MPL, CALR), but this entity is so rare that disease-specific clinical trials have proven difficult to conduct. However, anecdotes of favorable response to lenalidomide in RARS-T, even in the absence of del(5q), should prompt further investigation of the mechanism of response.⁹

To evaluate new therapies systematically, uniform response criteria are required. Consensus criteria to describe the response to nontransplant therapies in JMML have recently been published,¹⁰ but to date there have been no criteria for adult MDS/MPNs. MDS response criteria fail to capture the whole picture when, for example, a drug shrinks the spleen, yet anemia worsens. Is that a beneficial response or evidence of progressive disease? And although MPN response criteria address both cytopenias and organomegaly, improved

quality of life and possibly even survival with ruxolitinib use in patients who lack objective responses meeting IWG-MRT criteria highlight some of the limitations of response measures for such complex disorders.

The current proposal for MDS/MPNs by Savona and colleagues¹ recognizes that “clinical benefit” comes in many forms. These new criteria emerged from 3 workshops in which candidate measures were proposed, discussed, ranked, and revised. The authors tried to keep the new criteria as similar to familiar MDS and MPN response categories as possible, while recognizing the unique constellation of signs and symptoms faced by patients with MDS/MPNs. Importantly, the new criteria underscore the critical importance of patient symptoms, and the authors even propose 2 variants of “complete response”: with and without residual symptoms, measured with tools such as the familiar Myelofibrosis Symptom Assessment Form.¹¹ The origin of certain symptoms may be difficult to ascribe to MDS/MPNs vs another medical disorder (such as fatigue in some patients with comorbid conditions), which may cause practical problems in assigning a symptom response to the experimental therapy.

As with any new proposal, these criteria need to be prospectively validated, and only their use in the real-world clinical trial settings will demonstrate their value. As with many “consensus” guidelines and criteria, it is unclear how panel members were chosen beyond being a coalition of the willing, because there was no formal call for applications, and several active investigators in MDS/MPNs are missing from the author list. It is hoped that this omission will not impede the use and adoption of these criteria. A different group of investigators might have come up with slightly different criteria, but the chosen criteria address the most common patient complaints and most widely assessed disease markers in contemporary clinical practice.

Ultimately, response criteria are clinical Esperanto: communication tools that facilitate comparison of treatment

approaches and that make it easier for investigators to write therapeutic protocols, because home-brew response criteria no longer have to be generated for every study. Like all conversations, this one will evolve over time, but someone had to speak first.

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