Chronic myeloproliferative neoplasms

Managing myeloproliferative neoplasms evidence based on the ELN treatment recommendations 2018

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There are considerable advances in our understanding of the Philadelphia-chromosome (Ph)-negative myeloproliferative neoplasms (MPN) in the past 10 years including unraveling the mutation topography of these diseases, understanding the pathophysiology of myeloid proliferation and defining the role of inflammation in some of these disorders. There are also new therapy options and old therapies resuscitated. Moreover, improved health-related *quality-of-life* has become an important therapy goal.

However, although novel treatment strategies have been developed and sequential lines of therapy are currently available in clinical practice, several aspects of individual treatment decisions remained blurred and are still controversially discussed. The updated European LeukemiaNet (ELN) treatment recommendations of Barbui and colleagues [1] published in this issue of *Leukemia* concisely review the literature and provide a timely, comprehensive summary.

Diagnostic criteria for polycythemia vera (PV) were recently revised by the updated WHO definitions in 2016 [2]. One important diagnostic aspect is the lowered hematocrit and hemoglobin values appropriate to diagnose PV. Moreover, the need to perform a bone marrow study at diagnosis of PV (and any other type of MPN) is judged than before, and expert histology is suggested to precisely classify the MPN. Although phlebotomy remains the initial intervention in PV, its therapeutic limitations and the use of alternative therapies are debated. As there is no consensus definition of phlebotomy resistance, continuing frequent

phlebotomies to avoid drugs may result in iron deficiency. There is no recommendation for biomarkers to detect impending iron deficiency. Fine-tuning the frequency of phlebotomies to achieve iron-deficient erythropoiesis but avoiding severe iron deficiency is challenging. The current ELN recommendations highlight these severe iron deficiency syndromes by emphasizing the potential need for iron-supplementation in some cases. Still, careful reconsideration and thoughtful regulation of phlebotomy and modest iron depletion is important clinically because iron-supplementation of symptomatic patients is challenging and time-consuming. Hydroxyurea and recombinant interferon alpha are highlighted as first-line treatment options for high-risk, symptomatic persons and those poorly controlled by phlebotomy. Hydroxyurea-resistant or intolerant persons with PV may benefit from interferon alpha or a JAK-inhibitor.

The WHO definition of prefibrotic myelofibrosis as a new disease entity highlights the need to strictly adhere to the recent WHO diagnostic criteria. Distinguishing prefibrotic myelofibrosis from essential thrombocythemia (ET) is difficult and requires considerable expertise and possibly confirmation of bone marrow histology in a reference center. Use of the recently validated International Prognostic Score for ET (IPSET score), which includes the *JAK2*-mutation, thromboembolic events, age, and cardiac risk factors is recommended and better identifies persons at-risk. Panel members emphasized use of general risk factors for thrombosis should also be considered. Using the IPSET scoring system, the panel concluded that persons with ET and a *CALR* mutation do not benefit from anti-coagulation. Persons with high-risk ET should receive hydroxyurea, anagrelide, or interferon and possibly a JAK-inhibitor [3].

One of the most significant changes of WHO disease classification is revised diagnostic criteria for primary myelofibrosis in the context of the expanding mutation topography. Clinical prognostic scores such as IPSS, DIPSS, and DIPSSplus assess risk and will likely be supplemented by molecular analyses. The ELN update

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recommends detailed mutation analyses in persons who are *triple-negative*.

Ruxolitinib and transplants are therapy options in appropriate persons with MPN-associated myelofibrosis classified as intermediate-2- and high-risk. Choice between an early transplant vs. ruxolitinib is being addressed in clinical trials. How to treat persons in the intermediate-1-risk category is controversial. The FDA approval for ruxolitinib is for intermediate (no specification of intermediate-1 or -2) or high-risk myelofibrosis, whereas the European Medicines Agency (EMA) approval is for splenomegaly or constitutional symptoms [4, 5]. Persons with MPN-associated myelofibrosis with severe symptom burden may particularly benefit from the anti-inflammatory effects of ruxolitinib. The ELN panel highlighted possible use of ruxolitinib in persons with intermediate-1-risk, with symptomatic splenomegaly and a transplant in instances of therapy-resistance or additional risk factors (e.g., RBC-transfusion-dependence or high-risk mutations) in the context of a clinical trial.

In summary, the ELN recommendations provide thoughtful advice on how to diagnose and treat people with Ph-negative MPNs highlighting recent progress in diagnosis and therapy. However, as with any consensus statement we need to consider validity of their recommendations recalling there was once consensus on issues such as whether Earth was flat or the center of the Universe (Chinese astronomers had discarded such non-sense 2000 years before Galileo). Several commonly used medical therapies such as radical mastectomy or high-dose therapy and autotransplant for breast cancer recommended in expert consensus statements were later proved ineffective or even harmful when tested in randomized trials. The ELN document is an expert consensus statement, not a clinical practice guideline, which

requires much high-level data. With limited experience about new therapies registries and observational databases are useful to determine efficacy and safety. The ELN recommendations provide an excellent basis for future studies, which may answer outstanding questions and promote more personalized therapy of the Ph-negative MPNs.

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Compliance with ethical standards

Conflict of interest FHH has served as an advisory board member for Novartis Inc., AH received research support from Novartis, BMS, Incyte, and Pfizer; RPG is a part-time employee of Celgene Corp.

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