option, especially for patients with cytopenias and no neuropathy. BR is an effective chemotherapy regimen for WM, but myelotoxicity can be an issue in already cytopenic patients. Ibrutinib with or without rituximab can be used in first line or relapsed patients, but it seems to have a worse response in patients with wild type *MYD88*. Acalabrutinib and Venetoclax are other new options with response in relapsed setting, including in patient's refractory to ibrutinib. Zanubritinib, a new BTK inhibitor for WM treatment, is at least as effective as ibrutinib with perhaps a better toxicity profile.

Marginal Zone B-cell lymphomas (MZL)

The marginal zone B-cell lymphomas (MZLs) comprise extra nodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT), splenic MZL (SMZL) with or without villous lymphocytes and nodal MZL (NMZL) with or without monocytoid B cells. These are three distinct clinical entities with specific diagnostic criteria, clinical and therapeutic implications.

Regarding to localize H. pylori-positive gastric MZL, the initial treatment should be H. pylori eradication. This treatment can induce lymphoma regression and long-term clinical disease control in the most of 50% of the patients. In patients who do not achieve lymphoma regression following antibiotic therapy, and the rare ones not associated with H. pylori infections, radiotherapy seems to be the best choice (considering localized disease). Patients who require systemic treatment are not very common, but long-term data from the randomized study IELGS-19 showed better response rates and event-free survival when adding rituximab to chlorambucil, but no OS gain compared to chlorambucil alone[5]. SMZL in asymptomatic patients should be observed. There are no randomize trials, but when treatment is required, splenectomy and rituximab monotherapy are considered first-line. For asymptomatic patient diagnosed with NMZL is also recommended only observation. If systemic treatment is indicated, chemo-immunotherapy can be performed.

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ELN recommendations for treating MDS

David Bowen

Whilst peer-reviewed published guidelines have appropriate scrutiny and endorsement to support their validity, the reality is that these often become at least partially outdated soon after publication. In developing the latest iteration of guidelines for the diagnosis and management of MDS, the European LeukemiaNet MDS guideline group, has sought to create a web-based interface that is interactive, portable, and capable of dynamic updating at least annually. The guideline development process involved systematic literature review, expert opinion, and scenario analysis. The faculty was diverse; from 18 European countries. The group included Junior Faculty who fed back on content and the practicality for access from mobile devices. The final product is interactive and iterative, with upfront 'headline' recommendations supported by expanded information pages for readers requiring further detail [https://mds-europe.org/]. Examples of updates from our previous ELN guidance are:

Diagnosis: we suggest mutation analysis in all patients where available, to inform prognosis and management. We explain the strengths and the limitations of current knowledge, including discussion of the clonal cytopenias. We also include consideration of germline predisposition syndromes.

Prognosis: we provide calculation tools for IPSS-R and will update this with the forthcoming IPSS-Mol during late 2021/2022.

Low-risk MDS: we describe new data for iron chelation, for early use of Erythropoietic Stimulating Agents and for novel agents such as Luspatercept. Pathways for use of these agents are presented.

High-risk MDS: recommendations are given for the use of hypomethylating agents, chemotherapy, and allogeneic stem cell transplant. An interactive stem cell transplant algorithm including comorbidity is available to guide transplant decisions.

This project was supported by Horizon 2020 funding under the auspices of the MDS-RIGHT programme. The guidelines have recently been endorsed by the European Haematology Association. Discussions are ongoing with international colleagues such that the website may accommodate international variation of recommendations.

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How I treat Polycythemia vera

Barbara Mora, Frencesco Passamonti

Polycythemia vera (PV) is a Philadelphia-negative myeloproliferative neoplasms (MPNs),[1] characterized by high myeloid cells production secondary to mutations in Janus kinase 2 (JAK2) gene. [2,3] Incidence rate is higher in advanced age. [4]

Clinical phenotype is dominated by systemic symptoms, pruritus and microvascular disturbances; splenomegaly may be detected in 30-40% of cases. [5] In the long term, what impacts on outcome is the increased risk of thrombosis, evolution into post-PV myelofibrosis (PPV-MF), or into blast phase (BP). [6]

The main aim of PV treatment is preventing vascular events. [7,8] Patients are defined at high risk (HR) if they are older than 60 years or had a previous thrombosis, [7,8] but leukocytosis and high JAK2 allele burden might be of value. [9] Standard therapy for all PV patients includes phlebotomies, to maintain the hematocrit (Hct) below 45%, and aspirin. [10,11] For HR patients, cytoreduction must be added. [12] Therapy could also be started in case of signs of hyper-myeloproliferation (progressive leukocytosis, excessive thrombocytosis, splenomegaly), uncontrolled symptoms or intolerance to phlebotomies. [7,8] Hydroxyurea (HU) is the first choice in most countries since conventional interferons (IFNs) are burdened by numerous side effects. [13]

Pegylated forms (peg-IFNs) have been developed to improve tolerability through less frequent administrations. [14] Two recent phase 3 trials have investigated the potential benefits of first line peg-IFNs in HR PV patients. [15,16] The MPD-RC 112 study compared peg-IFN α-2a with HU. [15] At 24 months, peg-IFN was associated to a higher ORR (59.6%) compared to HU (40.7%). [15] The PROUD PV phase 3 trial was a randomized non-inferiority study between ropeg-IFN α-2b and HU. [16] The primary endpoint was composite: obtaining a complete hematologic response (CHR) and a normal spleen volume. [16] Given that few patients had baseline splenomegaly, the non-inferiority of ropeg-IFN was not apparent at 12 months. [16] The extension phase was named CONTINUATION PV. [16] At 36 months, the ropeg-IFN cohort obtained a significantly higher percentage of CHR with improved disease burden (52.6%) in comparison with the HU-treated one (37.8%). [16] Besides, continuing ropeg-IFN beyond one year was associated with sustained molecular response. [16] We suggest considering IFNs in young patients, fertile females, subjects without relevant vascular risk factors or massive splenomegaly.

About 15% of PV patients develops resistance/intolerance to HU. [17] The choice of a second line therapy should be based on patient's age and preferences, in addition to the current evidence on alternative treatments. [7,8] To date, the JAK1/2 inhibitor Ruxolitinib (RUX) and IFNs are the available options. Two prospective randomized studies, named RESPONSE [18,19] and RESPONSE-2 [20-22] evaluated PV patients resistant/intolerant to HU and in need of phlebotomy, with (RESPONSE) or without (RESPONSE-2) splenomegaly. [18-22] Primary composite endpoints were Hct control in the absence of phlebotomy (both studies) and 35% reduction in spleen volume (SVR) at week 32 (only for RESPONSE). [18-22] In the RESPONSE trial, the primary composite endpoint was achieved in 21% of patients in the RUX cohort vs. 1% on BAT. [18] Hct control was reached in 60% with RUX vs. 20% with BAT; SVR35 in 38% vs. 1% of patients. [18] A CHR was more frequently achieved with RUX (24% vs. 9%). [18] At five years, the probability of maintaining primary composite endpoint and CHR were 74% and 55%, respectively. [19] The five-years OS was comparable between arms (around 91%), but this analysis did not account for the extensive crossover. [19] The RESPONSE-2 study evaluated a "more conventional" PV population. [20-22] Hct control was reached in 62.2% of the RUX arm compared to 18.7% on BAT. [20] At week 80 and 260, the median duration of Hct control on RUX was 78% and not reached, respectively. [21,22] To note, in both studies the incidence of vascular events was lower in the RUX arm when compared to BAT arm. [19;22] In RUX treated patients we registered an high incidence of non-melanoma skin cancers (NMSC), [19,22], confirmed on a cohort of 151 RUX-treated secondary myelofibrosis. [24] The phase 2 MPD-RC 111 trial evaluated peg-IFN α-2a in 50 HR PV patients, resistant/intolerant to HU. [25] At 12 months, ORR and CR were 60% and 22%, respectively. [25] We find these results inferior compared to other trials on IFNs, probably because of the unfavorable features of the study population. [17] Thrombotic events occurred respectively in 2% and 5% of patients at one and two years, but the median follow up was only of 19.6 months. [25] We think that, based on the five-years follow-up, RUX appears to be effective as second line therapy, particularly in improving Hct or splenomegaly with a good control of thrombotic events.

Concerning low risk population, an interim analysis of the phase 2 randomized clinical trial LOW-PV, comparing standard therapy to the addition of ropeg-IFN α-2b in LR cases, has recently been published. [26] The primary composite endpoint of maintaining a Hct lower or equal to 45% for 12 months, without evidence of disease progression was reached in 84% of ropeg-IFN α-2b vs. 60% of standard treated patients. [26] Additionally, ropeg-IFN was associated with a reduction in phlebotomies need, symptoms burden and leuko-thrombocytosis. [28] Even though Hct control is often used as a surrogate of reduced thrombosis risk, we think that follow-up is presently too short to prove a protective vascular effect of ropeg-IFN α-2b in LR patients.

To date, there is little evidence that any of the available treatments might delay transformation into PPV-MF, which is associated with a substantial OS reduction. [27] An early detection of evolution into PPV-MF is therefore fundamental for optimizing treatment, especially for patients eligible to allogenic hematopoietic stem cells transplant (allo-HSCT). [7,8] Therefore, it is essential to carefully monitor patients for possible signs of transformation, as the development of anemia or splenomegaly. [28] Female patients seems to have a slower time to progression [29]. If PPV-MF is suspected, it is essential to perform a bone marrow evaluation and cytogenetic studies, since they have prognostic relevance. [30,31] PPV-MF survival is defined by the recently developed MYSEC-PM (MYelofibrosis SECondary to polycythemia vera and essential thrombocythemia-prognostic model). [32,33]. For patients below 70 years and in the higher MYSEC-PM categories, allo-HSCT outcome could be predicted by the MTSS (Myelofibrosis Transplant Scoring System) model. [34] The allocation of PPV-MF patients to allo-HSCT is therefore personalized. [35]

Future studies on PV treatment should focus on the pathogenesis of the disease and on possible pathways of progression, to prevent this unfavorable evolution. Special focus must be on familial cases of PV. [36]

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