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Editorial
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EHA Endorsement of the European Guidelines for Myelodysplastic Syndromes, MDS-RIGHT

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The European Hematology Association (EHA) recently agreed to endorse the guidelines on myelodysplastic syndromes (MDS) by the MDS-RIGHT (Providing the right care to the right patient with MDS at the right time) group (*MDS Europe - Patient management [https://mds-europe.org]*).[1] The MDS-RIGHT project is a large European project funded within the Horizon 2020 program and aimed at providing the right care to the right patient with MDS at the right time, and at developing well-accepted evidence-based guidelines. The project plunges its roots in the European MDS Registry (EUMDS, https://eumds.org/), a prospective multicenter European registry for newly diagnosed patients with MDS and MDS/myeloproliferative neoplasms, initiated in 2008 by a large group of hematologists collaborating in European LeukemiaNet (ELN, https://www.leukemia-net.org/) and currently involving 18 countries.

The MDS-RIGHT guidelines project lies on the robust basis of the evidence-based recommendations from the ELN, published in 2013, and provides an update on diagnosis, prognostic assessment, and treatment of primary MDS in adults (see Figure 1 for structure of the guidelines).[2]

Two key points characterize this initiative, making it a reference in the field of MDS in Europe: first, the project stems from the European MDS community, involving experts from 18 countries contributing to the MDS-RIGHT project and the EUMDS Registry, resulting in an unbiased, bottom-up process truly representative of clinical practice and standards of care across Europe. Second, these clinical practice guidelines were not developed based on a classical manuscript version, but by adopting a website-based approach to provide the means to a continuous update on a dedicated platform in a rapidly evolving field, while at the same time offering to the users a handy tool for real-time consultation. An editorial board is charged with yearly updates, which allows for up to date diagnostic and treatment decision making. Dynamic guidelines for MDS are required, as classification changes with every version of the World Health Organization (WHO) classification. Numerous proposals for diagnostic and prognostic classifications as well as for treatment are made in the time between publications of the WHO classifications in a recently rapidly evolving field.[3]

MDS patients are among the most frequent oncological patients hematologists will see during their career, as MDS is one of the most frequent hemato-oncological diagnoses taking into account the projected aging of the European population, and the estimated life expectancy of individuals with lower-risk MDS.[4] Diagnosis and treatment decisions, on the other hand, are not always straightforward and no single diagnostic tool is sufficient to make the diagnosis. A multitude of differential diagnoses have to be excluded, especially for low-risk MDS, and once the diagnosis is made, treatment decisions are no less challenging; ranging from watchful waiting or best supportive care only, to allogeneic stem cell transplantation. A common denominator in MDS is the presence of one or more cytopenias, which is mandatory but nevertheless not enough to make the diagnosis when present. Recently, newly defined conditions such as idiopathic cytopenia of uncertain significance, clonal hematopoiesis of indeterminate potential (CHIPs), and clonal cytopenia of uncertain significance are contributing to the difficult diagnostic work-up.[5] A bone marrow work-up is necessary to confirm the diagnosis, with emphasis on signs of dysplasia, blast count, and cytogenetic anomalies. Nowadays, oncogenomic analysis is mandatory for the work-up of a possible MDS case as cytogenetics are needed for the diagnosis of 5q-syndrome—a subtype of MDS with a relatively good prognosis—and next generation sequencing is needed in many cases to confirm MDS with ring sideroblasts if ring sideroblasts are below 15%. Furthermore, oncogenomics are essential to refine the prognosis and consequently, therapeutic decision making, and are very useful for follow-up, assessment of progression, and the aforementioned differential diagnoses such as CHIPs. In addition, some cytogenetic aberrations are defining for acute myeloid leukemia diagnosis, even if the blast count is below 20% as it is the case for MDS. It is also of utmost importance to rule out MDS with germline mutations or in the context of bone marrow failure syndromes, as the treatment choices have to be adapted considerably.

Having had for decades either best supportive care with transfusions and hematopoietic growth factors or intensive chemotherapy and allogeneic stem cell transplantation as more or less the only 2 extremes of treatment possibilities in a rather elderly patient population, more and more treatment options are emerging. First, hypomethylating agents (HMA) demonstrated a survival benefit when compared to best available

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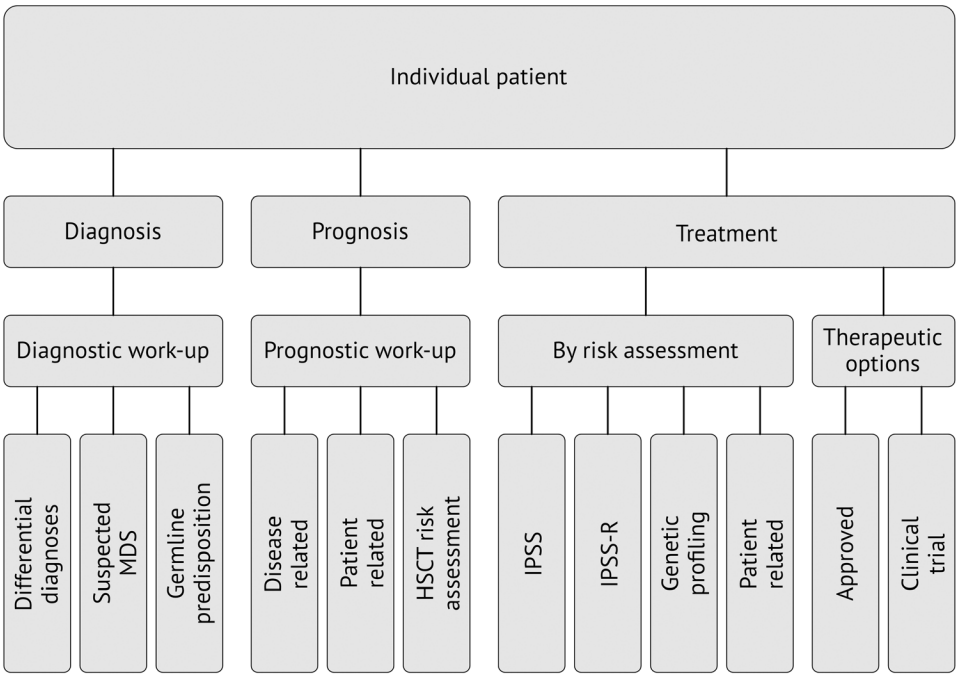

Figure 1. Individual patient algorithm. HSCT = haematopoietic stem cell transplantation; IPSS = international prognostic scoring system; IPSS-R = revised international prognostic scoring system; MDS = myelodysplastic syndrome.

therapy such as best supportive care, low dose cytarabine, or intensive chemotherapy,[6] and even if the data could not be consistently reproduced in the real life setting, HMA are nowadays a standard of care in high-risk MDS treatment to which all other new drugs have to compare. Also, lenalidomide joins the arsenal of available therapy for patients with the MDS subtype of 5q-syndrome.[7] More recently, additional treatments emerged, targeted to specific subtypes of MDS, such as luspartercept for MDS with ring sideroblasts.[8] Other targeted drugs such as isocitrate dehydrogenase inhibitors or fms-like tyrosine kinase 3 inhibitors, to name only a few, are currently tested in studies. Nevertheless, decision making for treatment remains challenging as age, performance status, and prognostic factors such as additional mutations of bad prognosis as with TP53 mutations, all have to be taken into consideration. It is most important to consider and follow the patient's wishes on different treatment options, particularly as we are dealing with a mostly elderly patient population of 70 years and over. Their vision of future treatment and expectance of quality of life versus intensity of the treatment should be paramount for the final treatment decision. It is important to note that this final step can never be replaced by guidelines.

As clinicians, may it be in private practice or in the university clinics, the individual patient is at the center of our concern. The MDS-RIGHT Clinical Practice Guidelines allows for the possibility to follow a step-by-step approach for the individual patient, from the diagnostic work-up over prognosis to the choice of treatment (Figure 1), but can also be used as a training tool for medical students, junior, and senior hematologists. The tool considers everything from differential diagnosis to germline mutations, prognostic work-up, and comorbidity scores for transplant. The board included junior faculty, who ensured flawless functionality on all kinds of electronic devices. Every hematologist confronted with MDS patients should follow the link and explore MDS Europe - Patient management (https://mds-europe.org).

Disclosures

The authors have no conflicts of interest to disclose.

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