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An Agenda to Advance Research in Myelodysplastic Syndromes: A TOP 10 Priority List From the First International Workshop in MDS

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COMMENTARY

blood advances

TO THE EDITOR:

An agenda to advance research in myelodysplastic syndromes: a TOP 10 priority list from the first international workshop in MDS

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Myelodysplastic syndromes (MDS) are neoplasms with high molecular, biological, and clinical heterogeneity.[1,2] Consequently, conducting basic, translational, and clinical research on MDS has historically been challenging and the field has lagged behind in terms of achieving significant therapeutic advances.

To advance research in MDS and translate those advances into clinical benefits for patients, the first international workshop for MDS (iwMDS) was conducted in Miami, Florida. Workshop participants represented a wide variety of international stakeholders in MDS across multiple disciplines. The workshop participants concluded that there is an overarching need for international and interdisciplinary collaboration and the coordination of research efforts. Here, we outline 10 critical areas that would benefit from broad collaborations (Table 1) and propose some concrete steps for future efforts (Table 2).

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Table 1. Top 10 list of MDS collaborative priority research goals

Priority research goals
1. To establish a new standard of care for frontline higher-risk MDS
2. To develop better treatment options for DNA methyltransferase inhibitor (DNMTi)-refractory MDS
3. To develop effective strategies for *TP53*-mutated MDS
4. To advance novel treatment strategies to impact the underlying pathophysiology of lower-risk MDS
5. To conduct clinical trials in a collaborative international effort with emphasis on equal access and on PROs
6. To formulate unified diagnostic criteria and classification subgroups for MDS
7. To establish and systematically validate clinically meaningful response criteria for MDS therapy
8. To establish tools to predict, and ultimately reduce, risk of progression of CH to MDS and other hematological malignancies in clinical practice
9. To establish linked clinical databases and biobanks allowing sharing of data
10. To improve the development and dissemination of reliable preclinical models of MDS

To establish a new standard of care for frontline higher-risk MDS

DNA methyltransferase inhibitor **(**DNMTi) monotherapy remains the standard of care therapy for higher-risk MDS.[3] Despite the established role of DNMTi therapeutics in MDS, several trials and real-world registry analyses have failed to replicate the survival benefit initially described with azacitidine in the AZA-001 trial.[4,5] To improve outcomes, multiple clinical trials have tested azacitidine (or DNMTi backbone) combination therapy approaches, but to date, none have improved overall survival (OS) compared with azacitidine monotherapy.[6-8] Hence, establishing a DNMTi backbone combination therapy for the frontline treatment of MDS is the top priority that has been identified by the faculty.

To develop better treatment options for DNMTi-refractory MDS

Outcomes for patients with DNMTi resistance are unfortunately dismal, with a median survival of <6 months and a 2-year survival probability of only 15% for patients with higher-risk MDS.[9] Outcomes for lower-risk patients with DNMTi resistance are also poor with a median survival of 17 months.[10] There is currently no standard

Table 2. Potential steps to achieve MDS priority research goals

Priority research goals	Action steps
1	- Development of new frontline treatment of MDS: Several large, randomized trials, including azacitidine in combination with the BCL-2 inhibitor venetoclax, the anti CD47 antibody magrolimab and the anti TIM3 antibody sabatolimab are ongoing
2	- Development of treatment options for DNMTi-refractory MDS: Several early phase clinical trials are ongoing; however, no therapy is approved yet at time of DNMTi resistance
3	- Develop trials with broad inclusion of both *TP53* mutated MDS and AML - Focus on trials with emphasis on engaging the immune system instead of chemotherapy based clinical trials - Utilize platform-based approaches to conduct multiple randomized phase II trials to establish a promising approach for phase III testing early (eg, NCI myeloMATCH)
4	- Palliative goals of treatment in LR-MDS are somewhat antithetical, considering that for patients with CH, a primary effort is to prevent the progression of disease. The focus of drug development should be on reversing the underlying pathophysiology of the disease. - One promising area of investigation is targeting immune dysregulation in MDS clones and the BM microenvironment (eg, targeting IRAK1/4 and/or the NLRP3 inflammasome)
5	- Expand eligibility to be representative and inclusive of the population including minority and underserved populations - Partner with pharmaceutical companies, government and regulatory agencies with a shared mission and set of goals - Inclusion of HRQoL and other type of PROs should always be considered for phase III trials to generate definite data that can facilitate clinical-decisions
6	- Formulate one single set of consensus diagnostic criteria (WHO classification has historically represented the gold standard in pathological classification)
7	- Update the International Working Group 2006 response criteria for higher-risk MDS with emphasis on association with long term benefit - Systematically and prospectively validate specific blood count cut-offs in response criteria - Eliminate response criteria without clear association with improvement in overall survival (eg, mCR without hematologic improvement)
8	- Secondary prevention of progression from CHIP to MDS in germ line predisposed, those receiving cytotoxic exposures, or acquired with age are all components of the same broader goal. - Develop practical decision-making tools to guide hematologists, medical oncologists, and patients alike in balancing the risks and benefit of adjuvant chemotherapy and radiation therapy in patients with high-risk CH
9	- Develop strategies to allow data sharing between large registries in the U.S. (National MDS Natural History Study and the Connect Myeloid Disease registry) and Europe (HARMONY Alliance and the MDS-RIGHT project) - Accomplishing these goals will require to overcome several bureaucratic and regulatory hurdles and necessitates sensitivity to the distinct privacy laws in Europe and the U.S.
10	- Utilize and widely distribute the improved in vivo modeling systems for MDS preclinical studies (eg, "MISTRG" mice)

treatment approach approved for these patients and clinical trial options are urgently needed, especially for patients who are not candidates for allogeneic hematopoietic stem cell transplantation.

To develop effective strategies for TP53-mutated MDS

TP53 alterations (deletions and mutations) are associated with extremely poor prognosis, with lower response to all established therapies, higher rates of progression to AML, and significantly shortened OS.[11] Even with allogeneic stem cell transplant outcomes remain poor.[12] Hence, international efforts should be focused on dedicated trials for this patient population as a holistic platform to also include *TP53*-mutated AML, which shares similar features with *TP53*-mutated MDS.[13] During the iwMDS, the NCI myeloMATCH program was presented which will include a multiarm phase II trial platform entirely dedicated to patients with *TP53* mutated MDS. Working groups developing directed algorithms for all *TP53*-mutated myeloid neoplasms should be considered given the dismal outcome for these disorders irrespective of blast percentage.[13]

To advance novel treatment strategies to impact the underlying pathophysiology of lower-risk MDS

In lower-risk MDS, the goal of treatment is to improve cytopenia, most commonly anemia. The standard of care remains supportive treatment with red blood cell transfusions, erythropoiesis-stimulating agents, luspatercept, lenalidomide for certain subtypes of LR-MDS, and DNMTis. However, "lower-risk" MDS is a misconception: while temporary benefit can be derived, these approaches do not have a significant disease-modifying effect, and therefore responses are of limited durability.[10] Future efforts should focus on attempting to reverse the underlying pathophysiology of MDS.[14,15]

To conduct clinical trials in a collaborative international effort with emphasis on equal access and on patient-reported outcomes (PROs)

Clinical trials should be conducted jointly in different countries to achieve rapid study completion. Trials should also promote health care equity for patients with MDS and focus on the inclusion of PROs. Collaboration among research groups worldwide will facilitate these research goals. In addition, the focus should be on optimizing the inclusivity of patients concerning eligibility criteria to encompass the older population of patients (eg, limited eligibility due to creatinine and or cardiac functions) that are currently frequently excluded, thereby hampering the investigation (and enrollment) of the population most afflicted with MDS.

To formulate unified diagnostic criteria for MDS

Recently the World Health Organization and the International Consensus Classification for myeloid neoplasms have published separate diagnostic criteria for AML and MDS.[16,17] Several important differences between the 2 classifications exist, especially in how patients with 10% to 19% blasts are classified.[18] There is a significant concern that having 2 separate classification systems could have a negative impact on clinical care and research and have the potential to create confusion among patients and providers, as well as in the design, conduct, and interpretation of clinical trials. The need to establish a unified consensus classification for MDS has been emphasized.

To establish and systematically validate clinically meaningful response criteria for MDS therapy

The current response MDS criteria suffer from significant limitations.[19,20] First, there is a clear inconsistency in how complete remission (CR) is defined for MDS based on the International Working Group 2006[20] compared with the definition of CR for AML in the ELN 2017[21] and ELN 2022[22] criteria. While no hemoglobin threshold is used for CR in AML, for MDS, CR requires a hemoglobin value $\geq$11 g/Dl, which has not been validated. These differences in CR definition can lead to different outcomes depending on which definition is used.[23] There is a need to develop and validate new response criteria for higher-risk MDS that capture meaningful clinical benefits, similar to the introduction of CR with partial hematological recovery in ELN 2022 AML criteria.[22,24,25] Conversely, the elimination of responses with doubtful clinical benefits (eg, marrow CR without meaningful count recovery) should be considered.[26]

To establish tools to predict, and ultimately reduce, risk of progression of clonal hematopoiesis (CH) to MDS and other hematological malignancies in clinical practice

The advent and widespread availability of next generation sequencing has led to the discovery of CH, which, in some cases, is associated with higher risks of cardiovascular disease[27] and hematologic malignancies.[28-30] Therefore, early intervention should be monitored and considered, especially among patients with solid tumors where high-risk CH clones can dramatically expand under the selective pressure of chemotherapy, increasing the risk of subsequent therapy-related myeloid neoplasms. We need to learn more about the genotypic and phenotypic characteristics of CH evolution to accurately predict which patients with CH will develop MDS and other blood cancers. Ultimately, the goal is to develop effective secondary preventive/therapeutic strategies that reduce the risk of aggressive hematologic malignancies and/or other CH-related diseases in patients with higher-risk CH lesions. The identification of CH before exposure to intensive chemotherapy or radiation therapy is not frequently covered by insurance companies, which is a barrier to obtaining adequate informed consent and poses risks to patients when deciding to embark on potentially toxic therapies. Lastly, how best to identify and classify patients with a germ line predisposition to develop myeloid malignancies such as MDS and AML, will be a significant future focus of genetic counseling and risk prevention efforts.[31]

To establish linked clinical databases and biobanks allowing sharing of data

Several large MDS registries have recently been developed to better understand the natural history of MDS and to establish large biorepositories. The global MDS community should establish a common minimum data set to enable data sharing across platforms. Achieving international alignment is essential for identifying and characterizing risk factors, clinical outcomes, and particularly drug responsiveness for subgroups of this rare disease, which are likely to be increasingly subdivided into more defined molecular subtypes.

To improve the development and dissemination of reliable preclinical models of MDS

Comprehensive in vivo preclinical studies of MDS have historically suffered from the limited ability of MDS stem cells to engraft in immunodeficient murine hosts. Recently, a patient-derived xenotransplantation model in cytokine-humanized immunodeficient "MISTRG" mice has been established, allowing disease modeling across MDS subtypes.[32] A broader availability of improved preclinical models and wider dissemination of these resources to laboratories around the world is critical to maximize the efficient evaluation of novel drugs and therapeutics in MDS.

We conclude that, given that MDS are rare and biologically heterogeneous blood cancers, there is an overarching dire need for international and interdisciplinary collaboration and coordination of research efforts. What became clear from this first iwMDS meeting was the necessity for the frequent continued exchange of ideas in a smaller informal setting that is more conducive to the creation of new collaborative efforts.

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