bjh commentary

'We cannot paint them all with the same brush': the need for a better definition of patients with myelodysplastic syndromes for clinical trial design

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Commentary on Duetz C, Cucchi DG, Polak TB, Janssen JJ, Ossenkoppele GJ, Estey EH, *et al.* The wider perspective: twenty years of clinical trials in myelodysplastic syndromes. *Br J Haematol.* 2022;**196**:329–335.

Myelodysplastic syndrome (MDS) is a puzzling disorder characterised by a highly heterogeneous pathobiology.[1] The modern availability of sophisticated platforms for mutational screening has opened a new molecular era shedding light on the genomic architecture of the disease and unravelling a plethora of genes associated with its pathogenesis.[2] Furthermore, the application of modern artificial intelligence approaches along with the availability of new and publicly accessible molecular data has helped understanding the diagnostic and prognostic implications of such information.[3] However, this improvement in MDS knowledge at a biological level has not been yet translated into an expansion of its therapeutic armamentarium as demonstrated by the fact that in the last 10 years only one drug (luspatercept) has been approved for the treatment of the disease (or better a specific subgroup).[4] When compared to acute myeloid leukaemia (AML), an inherently related disorder, the United States Food and Drug Administration (FDA)-approved drug list adds up to almost 10 new agents or formulations.[5] Along with such considerations, Duetz *et al.*[6] explored the history of the last 20 years of clinical trials in MDS, pinpointing the pitfalls of conducting clinical research in this field. In a retrospective analysis interrogating clinicaltrials.gov and clinicaltrialsregister.eu, the Authors identified 384 unique drugs in 426 phase I, 430 phase II and 48 phase III trials between 2000 and 2020. Agents aiming to ameliorate side-effects, regimens of graft-*versus*-host diseases after allogeneic haematopoietic stem cell transplantation (HSCT) and iron chelation therapies were excluded. The majority of the drugs were classified as 'targeted' (i.e. directed at disease-specific epitopes expressed on MDS cells) followed by hypomethylating agents. When compared to other haematological malignancies, the Authors found a low number of specifically MDS-directed clinical trials with an important fraction of studies being inclusive also of AML or related disorders in a basket-like fashion. In addition, when accounting for the Revised International Prognostic Scoring System (IPSS-R), a paucity of trials had been designed specifically for lower-risk (LR) MDS, although their incidence exceeds the one of higher-risk (HR) counterparts. One of the reasons explaining the discrepancy with the multitude of clinical trials for AML and the lack of original LR MDS studies is the near absence of *bona fide* preclinical models of MDS. Indeed, human cell lines and patient-derived xenografts are much better established for AML and HR MDS, whereas human LR MDS cells have lower rates of engraftment, undermining the difficulties of *in vitro* drug discovery and development.[7] The hindrances in drug designing are reflected by the analysis of Duetz *et al.*,[6] which identified that most MDS phase II studies did not have an MDS-only phase I but rather re-purposed agents explored in other malignancies with the aim of both identifying subgroups of responding patients and avoiding the extensive length from testing to final FDA approval of novel agents. However, such an approach is less likely to be fruitful in a biologically heterogeneous disorder such as MDS, especially for LR patients who represent around two-thirds of the MDS population.[8] In fact, the demographics of the disease (typically affecting individuals aged >70 years) pose challenges as to end-points to be studied and possible age-related toxicities. For this group of patients, re-purposed agents with well-known chemical identity and toxicities profiles might be

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an option. However, to date no existing drug is curative and the recourse to HSCT in this setting is limited because of the aforementioned MDS epidemiology.[9] Therefore, clinical trials have been focusing on transfusion dependency (main problem of LR disease) and risk of AML progression or survival in HR cases, neglecting, especially in phase III trials, important end-points such as quality of life (QoL), an essential aspect of care of elderly and frail patients. As a note, the Authors indeed emphasised that many MDS trials often failed to include QoL.

The formulation of future clinical trials may benefit from the availability of integrative big 'omics' data deriving from worldwide consortia, which, along with the newer acquisition on disease pathobiology, may open new scenarios for MDS trialists. For instance, the accessibility and costs reduction of whole genome and transcriptome sequencing data would enable the creation of 'digital twins' based on *in silico* network models of multiple disease-relevant variables allowing for testing new drugs in a timely, economical and safe fashion.[10] An example of an already existing triad of data (genomic, transcriptomic, *ex vivo* drug screening) is represented by The BEAT AML Master Trial effort (NCT03013998)[11] or the HARMONY Alliance initiative (molecular datasets and clinical trials). However, a *conditio sine qua non* to better define patients according to the specific genomic signatures underlying their disease is the incorporation of the new molecular information in the MDS World Health Organization (WHO)[12] classification and prognostication (Molecular-IPSS) models. These systems updates, which the entire MDS community is eagerly pursuing, will help in trials design and rational patient allocation, having the potential to be also cost-effective. Indeed, the dissection of the diverse clinically-defined R-IPSS risk groups is a major limiting factor in identifying patients' subcategories possibly responding to specific therapeutic interventions.[13] Whether sooner or later, the better understanding of the disease pathobiology will be fundamental to design precision drugs for MDS, judiciously group patients and offer them the best treatment option. Therefore, wide perspectives of clinical trials experiences represent an important framework to understand factors contributing to the paucity of available agents and guide drug expansion in clinical research. Ideally, in the future patients will be screened for their own genetic and epigenetic fingerprints to build drug-clustering approaches based on application of machine-learning algorithms, which will advise clinicians to better decide the best tailored treatment option.

Conflict of interest

The authors declare no competing interests.

References

1. Cazzola M. Myelodysplastic syndromes. *N Engl J Med*. 2020;**383**:1358–74.
2. Ogawa S. Genetics of MDS. *Blood*. 2019;**133**:1049–59.
3. Nagata Y, Makishima H, Kerr CM, Przychodzen BP, Aly M, Goyal A, et al. Invariant patterns of clonal succession determine specific clinical features of myelodysplastic syndromes. *Nat Commun*. 2019;**10**:5386.
4. Fenaux P, Platzbecker U, Mufti GJ, Garcia-Manero G, Buckstein R, Santini V, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med*. 2020;**382**:140–51.
5. Cucchi DGJ, Polak TB, Ossenkoppele GJ, Uyl–De Groot CA, Cloos J, Zweegman S, et al. Two decades of targeted therapies in acute myeloid leukemia. *Leukemia*. 2021;**35**:651–60.
6. Duetz C, Cucchi DG, Polack TB, Janssen JJ, Ossenkoppele GJ, Estey EH, et al. The wider perspective: 20 years of clinical trials in myelodysplastic syndromes. *Br J Haematol*. 2022;**196**:329–35.
7. Schmitt N, Jann J-C, Altrock E, Flach J, Danner J, Uhlig S, et al. Preclinical evaluation of eltrombopag in a PDX model of myelodysplastic syndromes. *Leukemia*. 2021. https://doi.org/10.1038/s41375-021-01327-w
8. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;**120**:2454–65.
9. Fenaux P, Haase D, Santini V, Sanz GF, Platzbecker U, Mey U. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up †*. *Ann Oncol*. 2021;**32**:142–56.
10. Björnsson B, Borrebaeck C, Elander N, Gasslander T, Gawel DR, Gustafsson M, et al. Digital twins to personalize medicine. *Genome Med*. 2019;**12**:4.
11. Burd A, Levine RL, Ruppert AS, Mims AS, Borate U, Stein EM, et al. Precision medicine treatment in acute myeloid leukemia using prospective genomic profiling: feasibility and preliminary efficacy of the Beat AML Master Trial. *Nat Med*. 2020;**26**:1852–8.
12. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;**127**:2391–405.
13. Pagliuca S, Gurnari C, Visconte V. Molecular targeted therapy in myelodysplastic syndromes: new options for tailored treatments. *Cancers*. 2021;**13**:784.