Why has it been so difficult to develop new drugs for MDS? A critical review and discussion of current approaches

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For the past century, the standard paradigm of drug development has included translation of basic research observations into human clinical trials, with successful trials then leading to broad availability of novel therapeutics. This approach has been remarkable effective at curing or slowing the progression of many diseases, extending the average human lifespan by decades.

However, some conditions have proven more difficult to develop new medicines for, including the **myelodysplastic syndromes (MDS)**, for which there remains a paucity of effective therapeutic agents in 2025 despite major advancements in treating other hematologic neoplasms. Over the past 30 years, only 7 drugs (azacitidine, lenalidomide, decitabine, decitabine/cedazuridine, luspatercept, imetelstat, and ivosidenib) have been approved by the FDA or EMA for use in MDS, and most patients with MDS will have no effective treatment options within 3 years from diagnosis. Investigators and sponsors have reported at least 17 negative randomized studies in higher-risk MDS populations since 2010; the only “positive” study in the higher-risk MDS subset was a trial of allogeneic hematopoietic stem cell transplant versus conventional care. We explore here the reasons behind this ongoing therapeutic gap and suggest some potential improvements in MDS drug development.

Clinical trials are essential for evaluating new drugs. There are many reasons that clinical trials fail, but here we focus primarily on MDS: 1) Disease **heterogeneity** and limited biology understanding has made identifying appropriate treatment targets difficult. 2) The **older age** of MDS patients means comorbidities and logistical problems can affect trial completion and limit long-term follow-up. 3) **The low prevalence** of MDS subsets such as those with particular DNA mutations has resulted in small sample sizes and inconclusive trial results. 4) The tested drugs in MDS have had both **efficacy** and **safety** problems that were not anticipated or seen in other populations. 5) Some sponsors have **moved too rapidly from phase I pilot studies to full development plans**. 6) Several studies have had **methodological problems**, such as excessively complex trial designs, inadequate eligibility criteria and irrelevant endpoints. **Endpoint** selection is critical, especially where overall survival may not be the most relevant measure. Surrogate endpoints like progression-free survival and transfusion needs are used, particularly in lower-risk MDS, but these can be problematic due to issues with definition and accuracy. The validity and clinical benefit of surrogate endpoints such as complete remission and minimal residual disease have been questioned. 7) Some study results may have been **misinterpreted**, based on a binary interpretation of p-values. Several examples of widely misinterpreted trials will be provided.

Even when clinical trials are successful and drugs are approved, **wide global adaption** of new approaches is not guaranteed. There are differences between real-world conditions and clinical trials, for example, including different populations

(younger and healthier in trials) and under-representation of certain populations in trials. As a result of all the negative trials, interest among sponsors in MDS may now be more limited, despite "orphan drug" programs and a large potential market. **New safety signals and toxicity** observed post-approval and survival data which do not confirm earlier trial results are also barriers, as is the high cost of contemporary drugs.

Several suggestions to improve the current situation are provided, including: I) **Continued research** to better understand MDS biology and identify more appropriate surrogate markers and endpoints. II) **Optimizing clinical trials** through simpler designs, appropriate statistical plans, and meaningful endpoints. III) **Closing the efficacy-effectiveness gap** between trials and real-world outcomes by broadening trial eligibility criteria and including under-represented populations. IV) Modernizing **facilitating programs** like orphan drug incentives and streamlining other regulatory interactions. V) Applying **artificial intelligence** and machine-learning tools to improve certain aspects of the drug development process.

In summary, a collaborative effort involving all stakeholders is necessary to refine the current paradigm and ensure that more patients can benefit from effective and available MDS medications, and that MDS does not continue to be a “backwater” of hematological malignancy treatments.