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Rethinking the effectiveness of hypomethylating agents in myelodysplastic syndromes: the 50%-2-year wall

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- MM reviewed the manuscript
- Both authors designed and wrote this editorial.

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- Both authors have no relevant disclosures
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In this issue of Haematologica, Xinping Zhou et al. present their multicenter trial assessing the addition of all-trans retinoic acid (ATRA) to decitabine (DEC) in the treatment of higher-risk myelodysplastic syndromes (HR-MDS), in an attempt to prolong overall survival (OS) [1]. They obtained higher overall response rate (ORR) but unfortunately, no survival advantage compared with DEC monotherapy. Thus, this report joins a long and frustrating list of hypomethylating agent (HMA)-based drug combinations that have failed to prolong OS of patients with HR-MDS.

HMAs, including azacitidine (aza) [2] and DEC [3], have become the standard first line treatments for patients with HR-MDS for the last 15 years. Aza has also shown a survival advantage. However, it has become clear from these and other trials as well as from real practice that these HR-MDS patients are not cured. Moreover, there is barrier that the response rate fails to exceed 50%, and that the duration is no more than 2 years. Thus, there is an unmet need to improve these outcomes.

How can we do better? Several approaches have been (unsuccessfully) taken, trying to overcome this barrier. This includes addressing the adverse effects, such as the related infections [4] or drug-related thrombocytopenia [5], as well as the introduction of novel or targeted agents [6,7]. The most popular strategy has been using HMA-based combinations, with the addition of another potentially effective drug. Unfortunately, so far all these trials, despite promising preclinical data or successful phase 1-2 trials, have been disappointing [see Table]. The recent disappointing trial was VERONA [8]; the addition of venetoclax to aza, while resulting in a higher ORR (76%), failed to prolong OS (22 months).

Xinping Zhou et al. have returned to all-trans-retinoic-acid (ATRA), an old agent that is effective in acute promyelocytic leukemia [9], and has shown activity in other myeloid disorders [10]. The different mechanism of action of ATRA suggests a synergistic effect with DEC. They randomized (1:1) 227 HR-MDS patients to receive either DEC monotherapy or the combination DEC-ATRA. Unfortunately, despite high complete response and ORR rates in the combination arm (23% and 78%, respectively), compared with DEC monotherapy (12% and 51%), OS was similar in both groups: 23.0 and 19.3 months, respectively (p=0.137).

Why have all these trials failed? How can we overcome the 50%-2-year wall? It is possible that the drugs are ineffective. However, the repeated failures raise the possibility of other explanations as well. We would like to make some suggestions.

It is possible that the tested combination(s) might be effective not in the whole patient population but in a certain subgroup of patients. The post hoc analysis of the VERONA trial, for example, suggested that younger patients might benefit from the aza-venetoclax combination [8]. Other agents might be suitable for other subgroups. This may lead to individualized therapy. Such a strategy requires many subgroup analyses, which demands high statistical power and larger numbers of patients in trials.

A tempting approach is to call upon our community to re-evaluate the current paradigm of drug development and clinical trials. Maybe it’s time to challenge the use of *classic* HMA for HR-MDS after 15 years? Recent reports point out that many

cancer trials suffer from limitations, including poor design and implementation, inadequate statistical planning, irrelevant endpoints, and overly strict eligibility criteria that leave out important patient subgroups and lead to misinterpretation of results. These pitfalls and caveats apparently lead to “failure” of the trials, associated with losing some effective therapies, when the trials are indeed wrongly defined as failures. Addressing these problems will not be easy or fast and will require collaboration among all stakeholders, including the regulatory authorities, the academic investigator community, the pharma industry and society.

This reevaluation does not exclude the continuation of research, aimed at detecting better targets and testing other approaches. A possible example is novel anti-inflammatory drugs that have recently been tested [11].

In parallel to the continuing the very important basic research and clinical investigation, this is a call for considering a paradigm shift. The time has probably come to challenge the 50%-2-year barrier that we have faced with HMA in HR-MDS over the last 15 years. Improving the quality of future clinical trials, both in design and in implementation, might lead to trials that are deemed *successful*. Success of these trials will hopefully be translated into more effective regimens that can be applied in practice.

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Table:

List of drugs given as a combination with hypomethylating agents and have failed to prolong survival in patients with higher-risk MDS

Drug	**Mechanism**	**Trial** (Name)	**Reference**
Lenalidomide	IMIDs	Vilen-01	Mittelman et al. Ann Hem 2016
Vorinostat	HDAC Inhibitor	North American Intergroup	Sekeres et al. J Clin Oncol 2017
Rigosertib	RAS/RAF/MEK + PL3K		Navada et al. Leuk Res 2018
Glasdegib	Hedgehog inhibitor		Savona et al. Clin Cancer Res 2018
Pevonedistat	NEDD8-Activ. enzyme inhibit.	PANTHER	Ades et al. Blood Adv. 2022
Durvalumab	PDL-1 Inhibitor		Zeidan et al. Blood Adv. 2022
Magrolimab	Anti-CD47	ENHANCE	Sallman et al. J Clin Oncol 2023
Sabatolimab	Anti-TIM3		Zeidan et al. Lancet Haematol 2024
Tamibarotene	RARA agonist	SELECT-MDS-1	DeZern et al. Blood Adv 2025
Venetoclax	Anti-Bcl2	VERONA	Garcia-Manero ASH 2025

Abbreviations: IMIDs – Immunomodulating agents; HDAC- Histon de-acetylating

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