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Correspondence on: Oral decitabine cedazuridine with and without venetoclax in higher-risk myelodysplastic syndromes or chronic myelomonocytic leukemia: a propensity score–matched study

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To the Editor,

In their retrospective analysis, Bataller et al. sought to evaluate the potential added benefit of incorporating venetoclax, a selective BCL-2 inhibitor, to the oral hypomethylating agent (HMA) combination decitabine and cedazuridine (DEC-C) in patients with higher-risk myelodysplastic syndromes (HR-MDS) or chronic myelomonocytic leukemia (CMML) [1]. Given the paucity of prospective randomized data directly comparing front-line regimens in this population—and the conceptual framework suggesting that MDS exists along a continuum of myeloid neoplasia with acute myeloid leukemia (AML)—there has been mounting interest in exploring whether venetoclax-based combinations might confer similar clinical benefits in MDS as those demonstrated in AML [2–5].

This oral combination offers a practical advantage over traditional intravenous decitabine-based regimens, enabling a fully outpatient, all-oral therapeutic option. To compare the efficacy and safety of the two treatment strategies, the authors conducted a post hoc analysis utilizing propensity score matching (PSM). Patients with HR-MDS or CMML who had received DEC-C in the context of two randomized phase 2/3 studies were matched to a cohort treated with DEC-C plus venetoclax from a single-institution phase 1/2 study. The authors subsequently compared clinical outcomes including overall response rate (ORR), time to best response, incidence and severity of adverse events, event-free survival (EFS), and overall survival (OS).

Their results indicated that patients treated with the combination regimen of DEC-C plus venetoclax achieved a significantly higher ORR by 2006 IWG criteria (complete remission + marrow complete remission: 90% vs. 64%; $p = 0.002$), shorter median time to best response (1.1 vs. 2.7 months; $p < 0.001$), superior EFS (18 vs. 10 months; $p = 0.026$), and were more likely to proceed to allogeneic hematopoietic stem cell transplantation (HSCT) (47% vs. 16%; $p < 0.001$). Although combination therapy was associated with more profound neutropenia, there was no difference in early mortality at 4 or 8 weeks. Notably, OS did not differ significantly between groups (24 months for DEC-C/venetoclax vs. 19 months for DEC-C monotherapy; $p = 0.89$).

Methodologically, the authors employed a nearest-neighbor matching approach without replacement using a caliper width of 0.2 and considered a standardized mean difference (SMD) < 0.1 as indicative of adequate balance. Their matching approach included age and the Molecular International Prognostic Scoring System (IPSS-M) score, which incorporates key clinical and biological covariates such as cytogenetic and molecular risk, bone marrow blast percentage, and peripheral blood counts.

We commend the authors for attempting to address a clinically significant and timely question. Nonetheless, we wish to underscore several important limitations inherent to the use of PSM in this context. Although PSM provides a method for reducing confounding in observational studies, its validity is contingent on several key assumptions—including the absence of unmeasured confounding, adequate overlap (positivity), and consistency. These assumptions may not hold in retrospective comparative analyses of treatments for HR-MDS/CMML, two biologically heterogeneous and clinically nuanced diseases.

Key considerations are critical for interpreting the results of this study. First, patients not receiving the DEC-C/venetoclax combination may have been subject to selection bias, potentially introducing confounding by indication. Treatment decisions in HR-MDS/CMML are influenced by risk assessments at diagnosis. As such, patients who were deemed frailer, with more significant comorbidities, might have preferentially received single-agent HMA, while those with more aggressive disease were more likely to receive combination therapy. This could have impacted outcomes, as disease biology in these two groups might have differed substantially. Additionally, it is crucial to consider the primary treatment goal for patients in the referential trials (HMA monotherapy versus DEC-C/venetoclax combination). It is plausible that transplant was not a therapeutic consideration for some patients receiving single-agent HMA, and that treatment was administered with non-curative intent, aiming instead to achieve long-term disease control. In contrast, patients who received the combination were more likely to achieve deeper responses and, consequently, proceed to transplant, further suggesting that transplant eligibility could have played a role in treatment choice. Unfortunately, without detailed information on patient characteristics such as frailty, comorbidity burden, or transplant eligibility, these nuances are not easily captured. These unmeasured confounders are essential to consider but often remain undetected unless explicitly accounted for in the study design.

PSM relies on conditional exchangeability. It assumes that all potential confounders are adequately captured in the selection of pretreatment variables. However, in practice, this is a challenging assumption to meet. Some factors influencing treatment decisions are simply not measurable or quantifiable through conventional data collection methods. These unmeasured confounders—instrumental variables— while not directly influencing the treatment outcome, influence treatment selection and, by extension, affect the observed outcome. As such, a critical

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question remains: why were certain patients chosen to receive combination therapy rather than monotherapy? An instrument variable analysis could have been used to address this issue and provide a clearer understanding of the underlying treatment selection process and its impact on the observed results.

In addition to these aspects, the following points merit further consideration:

1. **Lag Time and Data Maturity**: The shorter follow-up duration in the combination therapy cohort limits the capacity to assess long-term outcomes. The authors acknowledge this limitation, noting that the median follow-up time for the combination cohort was only 16 months, compared to 29 months for the HMA monotherapy cohort. Immature survival data may obscure potential survival differences due to the longer observation period in the more established monotherapy cohort.
2. **Immortal Time Bias** is another important limitation inherent in studies of this nature and refers to a period during which patients must survive to be eligible for treatment assignment, potentially making one treatment appear more effective simply because patients must live long enough to receive it. If not properly accounted for, this could lead to the artificial inflation of EFS in the combination therapy cohort if treatment initiation was delayed relative to the HMA monotherapy cohort.
3. **Matching on Baseline Covariates Only and Time-Dependent Confounding**: In HR-MDS, disease evolution and dynamic risk factors can shift rapidly. Consequently, initial baseline covariates may not fully reflect biological or clinical changes that influence subsequent outcomes. PSM adjusts for baseline characteristics but may inadequately account for biologically significant differences that emerge during treatment. Furthermore, covariates that are part of the IPSS-M change over time and influence treatment decisions. PSM, being a baseline adjustment method, is not designed to address time-dependent variables, such as evolving cytopenias or changes in transfusion requirements, which could affect treatment intervals or necessitate modifications to venetoclax dosing.
4. **Potential Heterogeneity in Venetoclax Use**: Possible heterogeneity in the use of venetoclax within the combination cohort introduces further complexity to the interpretation of the results. Variability in treatment administration, such as differences in dosage, may confound the assessment of the treatment's true effect.
5. **No Control Over Post-Treatment Variables**: PSM does not account for post-treatment interventions, such as subsequent transplantation, dose modifications, or supportive care. Post-baseline management can influence survival and other outcomes. Additionally, differential censoring or variations in post-treatment therapies can introduce bias in effect estimates.

CONSIDERATIONS REGARDING CMML

Approximately 25% of the study population comprised patients with CMML, a disease entity that, while overlapping with MDS in some clinical features, is biologically distinct. Prior studies have suggested that CMML may respond less favorably to venetoclax-based combinations [6, 7], potentially due to differential apoptotic dependencies such as reliance on MCL-1 over BCL-2 as has been identified in monocytic AML [8]. Including CMML patients in aggregate analyses risks diluting or distorting outcomes specific to HR-MDS and precludes disease-specific conclusions. Risk stratification and treatment decisions in CMML are optimally guided by disease-specific algorithms rather than extrapolated from MDS paradigms [9].

POST-TRANSPLANT OUTCOMES

The study demonstrated no difference in post-HSCT outcomes—including OS, EFS, and relapse incidence—between treatment groups. Furthermore, when patients were censored at the time of transplant, survival differences were similarly null, underscoring that transplantation remains the only curative modality in this setting. Therefore, the principal clinical value of the combination regimen may lie in its potential to deepen responses and increase transplant eligibility, rather than in offering a long-term survival advantage over monotherapy.

IMPLICATIONS IN LIGHT OF THE VERONA TRIAL

These findings must be interpreted in the context of the recently reported phase 3 VERONA trial, which failed to demonstrate a survival benefit for HMA/venetoclax over HMA monotherapy in HR-MDS [10]. These results compel a reassessment of previous assumptions derived from early-phase observations favoring venetoclax-based combinations and underscore the need to critically analyze response assessment criteria and patient selection methodologies. One hypothesis emerging from these results is the potential overemphasis on marrow CRs as a surrogate for long-term clinical benefit. It appears that marrow CR may be an unreliable metric, potentially inflating expectations regarding what constitutes a meaningful or sufficient response. Marrow CR, in isolation, may not reflect true restoration of hematopoietic function or translate into superior clinical outcomes [11].

As we move forward, both current and future investigative efforts will likely focus on more stringent and clinically relevant response assessment measures. This approach will aim to better define therapeutic success and hopefully identify effective treatment strategies for higher-risk MDS/CMML, ultimately working toward the elusive goal of improving survival and long-term outcomes in this challenging population.

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AUTHOR CONTRIBUTIONS

L.E.A. conceived and drafted the correspondence, conducted the critical appraisal of the study methodology, and integrated the supporting literature. M.S. contributed to the conceptual framing and provided intellectual input during manuscript refinement. R.M.S. and D.D.A. contributed to the conceptual development of the correspondence and provided expert review and critical feedback on the final version. All authors approved the manuscript before submission.

COMPETING INTERESTS

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Luis E. Aguirre reports consultancy for Curio Science, Cardinal Health, Research To Practice. Honoraria from Curio Science, Fast4ward Learning, Cardinal Health, DAVA Oncology. Richard M. Stone reports research funding from Janssen and AbbVie; Consultancy for GlaxoSmithKline, Curis Oncology, Daiichi Sankyo, ENSEM, Epizyme, BerGenBio, AMGEN, Syntrix, Hermavant, Glycomimetrics, CTI Biopharma, Bristol Meyers Squibb, Rigel, Syndax, AvenCell, Takeda, Jazz, Kura Oncology, Lava Therapeutics, Cellarity, Ligand Pharma, Novartis, Aptevo, and Redona therapeutics; Other: DSMB for Epizyme, Syntrix, Takeda, and Novartis. Daniel J. DeAngelo reports consultancy for Kite, Servier, Incyte, Pfizer, Gilead, Novartis, Jazz, Autolos, Amgen, and Blueprint; Honoraria from Amgen and Bristol-Meyers Squibb; Research funding from Servier, Novartis, Glycomimetics, AbbVie, and Takeda; Other: DSMB for MT Sinai MPN Consortium, Fibrogen, Daiichi-Sankyo. Maximilian Stahl reports membership on the Board of Directors or advisory committees for GSK, Rigel, Sobi, Sierra Oncology, Kymera, BMS, and Syndax. No other disclosures were reported.

ADDITIONAL INFORMATION

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