Efficacy And Safety Of Venetoclax Plus Azacitidine For Patients With High-Risk Myelodysplastic Syndromes - A Meta-Analysis

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Introduction

- High-risk myelodysplastic syndromes (MDS) are associated with poor prognosis and limited response to standard hypomethylating agent (HMA) therapy, necessitating improved treatment strategies.
- Venetoclax, a BCL-2 inhibitor, in combination with azacitidine or decitabine, has shown promising efficacy and higher response rates in high-risk MDS, both in clinical trials and real-world studies, but is associated with significant myelosuppression and infectious complications[1-2]

Aim

- To assess whether venetoclax + azacitidine improves clinical outcomes (response rates, transfusion independence, bridge-to-transplant) in high-risk MDS, while defining its safety and toxicity profile.

Methods

- **Search strategy:** PubMed, Cochrane, and clinicaltrials.gov for studies of **venetoclax + azacitidine** in HR-MDS.
- **Endpoints analyzed:**
  - Efficacy → CR, marrow CR (mCR), modified overall response (mOR), hematologic improvement (HI), transfusion independence (TI), progression to AML, SCT utilization, and mortality.
  - Safety → grade 3/4 treatment-emergent adverse events (TEAEs), including neutropenia, thrombocytopenia, anemia, febrile neutropenia (FN), pneumonia, and sepsis.
- **Statistics:** Mantel–Haenszel method, random-effects model, pooled effect sizes with **95% CI**, significance at $p < 0.05$.

Figure 1: Complete response

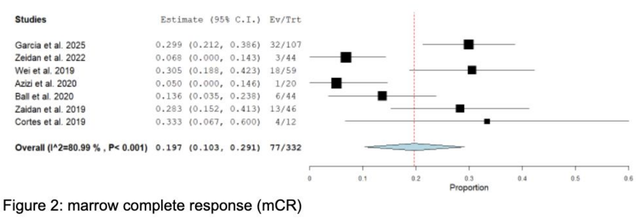


Figure 2: marrow complete response (mCR)

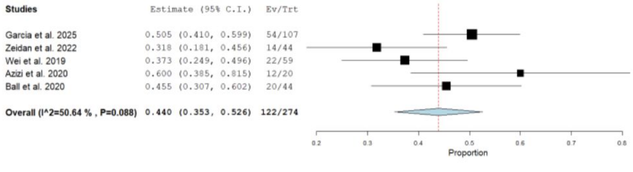
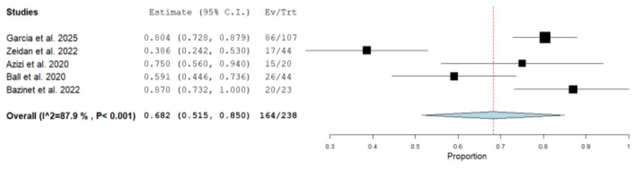


Figure 3: modified overall response (mOR)



Results

Meta-analysis included **9 studies**: 4 early-phase clinical trials and 5 retrospective cohorts of patients with **high-risk or relapsed/refractory MDS**. All evaluated **venetoclax (14–28 days) + azacitidine/decitabine**, reporting outcomes on **response, transfusion independence, AML progression, SCT, and safety**.

Efficacy

- **Modified Overall Response (mOR):** 68.2% (95% CI: 51.5–85.0, p < 0.001)
- **Marrow CR (mCR):** 44.0% (95% CI: 35.3–52.6, p < 0.001)
- **Complete Response (CR):** 19.7% (95% CI: 10.3–29.1, p < 0.001)
- **Hematologic Improvement (HI):** 34.3% (95% CI: 16.5–52.2)
- **Transfusion Independence (TI):** 28.1% (95% CI: 14.7–41.5)
- **Progression to AML:** 14.7% (95% CI: 7.4–22.1)
- **Bridge to SCT:** 24.3% (95% CI: 11.7–36.8)

Safety

- **Grade 3/4 TEAEs:** 96.9%
- Most common:
  - Neutropenia (45.2%)
  - Thrombocytopenia (39.8%)
  - Anemia (31.1%)
  - Febrile neutropenia (31.4%)
  - Pneumonia (19.1%)
  - Sepsis (3.4%)

Discussion

- Venetoclax + azacitidine shows promising efficacy in high-risk MDS, with higher response rates compared to historical HMA monotherapy.
- Benefits include transfusion independence (~28%) and use as a bridge to stem cell transplant (~24%), supporting its disease-modifying potential.
- Toxicity burden is substantial, with nearly all patients experiencing grade 3/4 adverse events, mainly cytopenias and infections.
- Careful monitoring and supportive care are essential to manage complications and optimize outcomes.
- Limitation: Results are based on heterogeneous, mostly single-arm or retrospective studies, with no randomized controlled comparisons.

References

1. Impact of Venetoclax on High-Risk Myelodysplastic Syndromes: A Retrospective Multicenter Analysis of Azacitidine-Venetoclax vs Azacitidine Monotherapy in Mexico Clinical Lymphoma, Myeloma and Leukemia, Volume 24, S396 - S397
2. A phase 1b study of venetoclax and azacitidine combination in patients with relapsed or refractory myelodysplastic syndromes.American journal of hematology vol. 98,2 (2023)

SOHO ANNUAL MEETING 2025