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Guadecitabine therapy following treatment failure with azacitidine in patients with acute myeloid leukemia

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The treatment for elderly patients with high-risk myelodysplastic syndrome and low blast count acute myeloid leukemia (AML) involves the hypomethylating agents (HMA) azacitidine and decitabine.[1] Azacitidine treatment failure results in poor survival for patients with high-risk relapsed/refractory (R/R) AML.[2] The novel second-generation HMA guadecitabine (SGI-110) allows for extended decitabine exposure due to the dinucleotide structure and degradation resistance.[3] This provides the opportunity for guadecitabine to be used as salvage therapy for patients ineligible for stem cell transplantation or intensive chemotherapy.

Marie Sébert from Hématologie Clinique, Hôpital Saint-Louis, Paris, France, and colleagues conducted a multicenter phase II (NCT02197676) study to evaluate the efficacy and safety of guadecitabine in patients with high-risk myelodysplastic syndrome and low blast count R/R AML (n = 56; median age = 75 years; range, 69–76), who have failed azacitidine therapy.[1] Patients received (n = 55) subcutaneous guadecitabine (60 mg/m^2/d, days 1–5 of 28-day cycle) therapy until progression, no response, toxicity, or death. The primary endpoint of this study was to assess hematological response.

Key findings:

- Patient characteristics at baseline:
  - Median prior azacitidine treatment cycles: 13 (range, 6–23)
  - Patients relapsing after a response to azacitidine: 73% (41/56)
  - Patients with primary resistance to azacitidine: 27% (15/56)
  - Patients with ≥ one somatic mutation: 87.5% (49/56)
    - Most common mutations include: *ASXL1* (n = 1; 25%), *RUNX1* (n = 12, 21%), *TP53* (n = 11, 20%), *U2AF1* (n = 11, 20%), and *DNMT3A* (n = 11, 20%)
- Efficacy of guadecitabine therapy
  - Patients responding to guadecitabine therapy: 14.3% (8/56)
    - Responses included: complete response (CR, n = 2), partial response (PR, n = 1), marrow CR (n = 2) and stable disease with hematological improvement (HI, n = 3)
    - Responses seen in 26% (4/15) patients with primary azacitidine failure, and 9% (4/41) patients with relapsing disease, *P* = 0.12
  - Median duration of response: 11.5 months (95% CI, 9–not achieved)
  - Median overall survival (OS): 7.1 months (95% CI, 5.6–11.8)
    - Median OS in patients responding to guadecitabine: 17.9 months

- One-year survival rate: 33% (95% CI, 22.9–48.4)
- Response rate was significantly higher in patients with no detectable somatic mutations compared to patients with ≥ 1 somatic mutation, *P* = 0.036

- Safety
  - Patients in which death occurred: 49
    - Causes for death: progressive disease (57.1%, 28/49), infection (26.5%, 13/49), bleeding (2/49), heart failure (1/49), and unknown (5/49)
  - Number of serious adverse events occurring in 44 patients: 99
    - Of which, 88% were due to hematological or myelosuppression causes
  - Grade III-IV non-hematological toxicities occurred in ≥ 3% patients

In conclusion, the study authors suggested that guadecitabine therapy may be beneficial to some patients following azacitidine therapy failure. Additionally, the results indicate that patients with primary azacitidine failure may be better candidates for guadecitabine therapy than patients with secondary azacitidine failure.

References

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