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FLT3

Sorafenib in combination with azacitidine in older patients with *FLT3-ITD* mutated acute myeloid leukemia

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Sorafenib in combination with azacitidine have been shown to be well tolerated and effective in older patients with relapsed/refractory FMS-like tyrosine kinase 3–internal tandem duplication (*FLT3-ITD*) acute myeloid leukemia (AML).[1] Based on this, a group of researchers from the MD Anderson Cancer Center, Houston, Texas, investigated the safety and efficacy of sorafenib, a multi-kinase inhibitor with significant FMS–like tyrosine kinase 3 (*FLT3*) inhibitory activity, in combination with azacitidine in older patients who are unsuitable for standard chemotherapy with newly diagnosed *FLT3-ITD* mutated AML. The results of this study were published in the American Journal of Hematology in July 2018.[2]

In this study, 27 patients (median age = 74 years; range, 61–86) with newly diagnosed untreated AML who underwent frontline therapy in two separate clinical trials (NCT02196857 [phase II portion of a phase I/II study] and NCT01254890 [phase II study]) were included. Patients were treated with a regimen consisting of azacitidine (75 mg/m^2 daily for 7 days) and sorafenib (400 mg twice daily). Patients underwent a median of three (range; 1–35) treatment cycles.

Key findings:

Efficacy

- Overall response rate: 78% (21/27)
  - Complete response (CR): 26% (7/27)
  - CR with incomplete recovery of peripheral blood counts (CRi)/CRp: 44% (12/27)
  - Partial response: 7% (2/27)
- Median time to achieve response: 1.8 months (range, 0.62–4.96 months)
- Median duration of CR/CRp/CRi: 14.5 months (range, 11–28.7 months)
- Three responding patients (11%) proceeded to allogeneic stem cell transplantation
- Median follow-up time: 4.1 months (range, 3.0–17.3 months)
  - Median overall survival (OS): 8.3 months (range, 1–63 months)
  - Median OS in responders (n = 19) and non-responders (n = 8): 9.2 (range, 2 – 63) *vs* 2.8 (range, 1–9) months, respectively, $P = 0.007$
  - Median relapse-free survival in all patients: 7.1 months (range, 1–29 months)

Safety

- The most common grade 1–2 adverse events (AEs) were hyperbilirubinemia (22%), diarrhea (22%), fatigue (22%), and nausea (19%)
- The most common grade 3–4 AEs were infections (26%) and neutropenic fever (26%)
- There were no early deaths recorded within 14 days of the study

In summary, findings of this study suggests that the combination of sorafenib and azacitidine is "well tolerated" and effective in older patients with newly diagnosed *FLT3-ITD* mutated AML. The authors noted that the results of this study were "encouraging".

Key limitation of this study includes the small sample size. The researchers recommend larger studies that can examine fully the benefit of sorafenib plus azacitidine in elderly patients with AML.

References

1. Ravandi F. *et al*. Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. Blood 2013; 121: 4655–4662. DOI: 10.1182/blood-2013-01-480228. Epub 2013 Apr 23.
2. Ohanian M. *et al*. Sorafenib Combined with 5-azacytidine (AZA) in Older Patients with Untreated FLT3-ITD Mutated Acute Myeloid Leukemia (AML). Am J Hematol. 2018 Jul 20. DOI: 10.1002/ajh.25198. [Epub ahead of print].