

Survival for the fittest: guadecitabine in rel/ref AML

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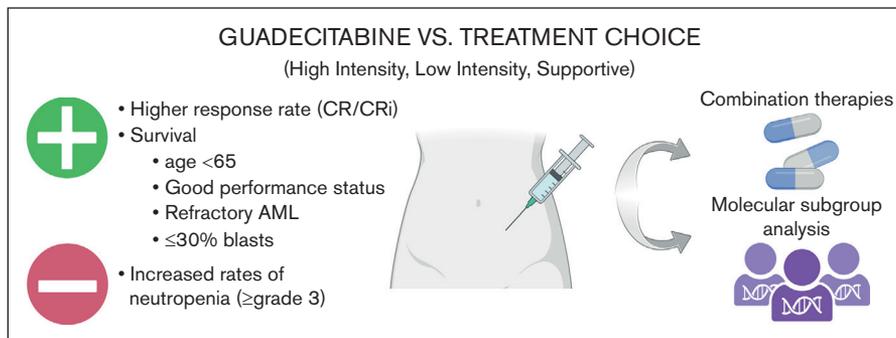
Relapsed or refractory acute myeloid leukemia (AML) has an extremely poor prognosis because of intrinsic chemotherapy resistance and high rates of relapse, even after allogeneic bone marrow transplantation. In this issue of *Blood Advances*, Roboz et al¹ report the results of the ASTRAL-2 prospective, international, multicenter randomized phase 3 clinical trial examining the effects of guadecitabine vs preselected physician's treatment choice for patients with relapsed or refractory AML.

Relapsed or refractory AML has a 5-year survival rate of <10%, and the current treatment paradigm is largely guided by patient fitness and comorbidities. For medically fit, younger patients, high-intensity salvage regimens based around intermediate or high-dose cytarabine in combinations with an anthracycline or other chemotherapy, are used to induce remission with the goal of allowing allogeneic stem cell transplant. However, the use of these approaches may be constrained by patient comorbidities, age, or preference. In the presence of mutations in driver oncogenes, such as internal tandem duplication of FMS-like tyrosine kinase-3 (FLT-3 ITD) or isocitrate dehydrogenase (IDH1/2), targeted approaches to inhibit the activity of these oncogenes may be more effective than chemotherapy. For patients who cannot tolerate high-intensity therapy, the mainstay of treatment is either low-dose cytarabine (LDAC) or hypomethylating agents, such as azacitidine or decitabine, sometimes combined with venetoclax (a B-cell lymphoma-2 (BCL-2) inhibitor).² However, neither of these approaches are curative, and given the poor survival in relapsed or refractory AML, there is an urgent, unmet clinical need for new therapies.

In a recently published manuscript, the efficacy of guadecitabine was evaluated in newly diagnosed AML. Guadecitabine is a novel hypomethylating agent that is a dinucleotide of decitabine and deoxyguanosine, which is therefore resistant to degradation of cytidine deaminase and has a prolonged half-life.³ When compared to standard-of-care in newly diagnosed AML (the ASTRAL-1 trial),⁴ guadecitabine showed no overall survival benefit for the cohort, but demonstrated an overall survival benefit in post hoc analysis for patients who were able to tolerate 4 cycles of treatment. Guadecitabine therapy was associated with increased rates of grade 3 neutropenia.

Concurrently, guadecitabine was evaluated in patients with relapsed or refractory AML. In the current ASTRAL-2 study, Roboz et al recruited 302 patients with relapsed or refractory AML across 98 centers in 15 countries. The patients were randomized to guadecitabine or treatment choice, in which treatment choice was preselected as either low-intensity therapy (77%), high-intensity therapy (21%), or best supportive care only (2%). With a median follow-up of 21.6 months, the study did not observe any significant difference in the primary end point of overall survival between guadecitabine (6.4 months) and either of the treatment choice groups; high intensity (6.2 months) or low intensity (5.3 months). However, across the cohort, there was an improved complete response (CR) with guadecitabine vs treatment choice (13% vs 7%) and significantly higher CR with partial hematologic recovery (17% vs 8%, $P = .01$) and CR with incomplete hematologic recovery (27% vs 14%, $P < .01$). In the relapsed or refractory setting this improvement in response rate may translate into a higher number of patients who can be subsequently offered allogeneic transplantation.

Intriguingly, guadecitabine showed improved survival for subgroups reflecting who are patients generally fit who were able to tolerate therapy—those aged <65 years, those with Eastern Cooperative Oncology Group performance status of 0 to 1, and those who received ≥ 4 cycles of treatment, consistent with the findings from ASTRAL-1. Those with refractory AML and those with $\leq 30\%$ peripheral blasts also showed a survival benefit. In terms of adverse events, guadecitabine had a significantly higher rate of grade ≥ 3 neutropenia vs treatment choice (32% vs 17%), but no increase



Guadecitabine vs treatment choice in patients with relapsed or refractory AML demonstrates higher response rates and favourable survival outcomes in certain subgroups. This is at the expense of higher toxicity (neutropenia).

in febrile neutropenia. This likely reflects that guadecitabine is more potent than the low-intensity treatments that were used in the majority of patients in the control cohort; a finding that may also explain the higher response rates (see figure).

These findings fall short of establishing guadecitabine as a new standard-of-care in patients with relapsed or refractory AML. However, improved complete response rates in a disease with such dismal outcomes raises the possibility that guadecitabine could serve as a novel backbone in combination with other therapies. Specifically, BCL-2 inhibitors are often combined with hypomethylating agents, such as azacitidine or decitabine and have substantial activity in newly diagnosed AML. This is evidenced by the phase 3 randomised placebo-controlled trials VIALE-A⁵ and VIALE-C.⁶ These trials demonstrated that venetoclax combined with azacitidine or LDAC improved response rates and survival for newly diagnosed patients with AML who were ineligible for high-intensity chemotherapy. Targeted inhibitors for subgroups with mutations in FLT-3 or IDH, as well as many other agents under current exploration, also represent a growing body of evidence in both the de novo and relapsed or refractory AML cohorts.² Finally, molecular markers are critical in determining outcome in AML,⁷ and there is an opportunity to pursue deeper molecular analysis of responding patients in this cohort as well as the ASTRAL-1 cohort. Identifying molecular biomarkers of response may further improve efficacy of this agent through precision approaches, and exploration of this may form the basis of future studies.

Conflict-of-interest disclosure: S.W.L. has received consulting fees from AbbVie (venetoclax) and research funding from Bristol Myers Squibb (azacitidine). J.S. declared no competing financial interests.

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<https://doi.org/10.1182/bloodadvances.2024012569>

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