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Evaluating a Lower-Intensity Treatment Regimen in AML: Phase 2 Results from PARADIGM

Ryan Quigley:
You're listening to *Project Oncology* on ReachMD, and this is an *AudioAbstract*. I'm Ryan Quigley, and today, we'll be diving into new phase 2 data from the PARADIGM trial, which was presented at the 2025 American Society of Hematology Annual Meeting.

For decades, the standard for treating fit adults with newly diagnosed acute myeloid leukemia has been intensive chemotherapy. But even for younger, healthier patients, these regimens come with real costs, including serious side effects, long hospital stays, and outcomes that still fall short. But new findings from the PARADIGM trial have the potential to reshape this treatment approach.

This phase 2, randomized study asked whether azacitidine and venetoclax—a lower-intensity, outpatient regimen already used in older adults—could actually outperform intensive chemotherapy in eligible patients.

PARADIGM enrolled 172 adults across nine U.S. centers. Everyone included was considered fit enough for induction therapy. But to keep the risk profile consistent, the study excluded patients with favorable tumor biology, such as core binding factor fusions or *FLT3* mutations.

Participants were randomized to receive either azacitidine with venetoclax or standard chemotherapy, which could either be 7+3 or CPX351. Consolidation and stem cell transplant were permitted in both arms based on response.

Now, let's take a look at the findings. At a median follow-up of 16 months, patients treated with azacitidine and venetoclax had an improved one-year event-free survival rate of 53 percent versus 39 percent for induction chemotherapy as well as improved overall event-free survival at a hazard ratio of 0.61. They were also significantly more likely to respond to treatment, and a greater proportion proceeded to stem cell transplant, suggesting that the regimen not only helped patients achieve remission but also bridged them toward potentially curative therapy.

Importantly, early mortality was lower with azacitidine and venetoclax. No patients died in the first 60 days, compared to several deaths in the chemotherapy group. Serious infections like sepsis and pneumonia occurred less often in the azacitidine-venetoclax group, and no patients required ICU care, compared to about one in ten in the chemotherapy arm.

Hospitalization time was another notable difference. Patients treated with azacitidine and venetoclax spent significantly less time in the hospital, cutting the initial inpatient stay by more than half and saving over two weeks across the first six months.

And at just two weeks into treatment, patients receiving azacitidine and venetoclax reported better quality of life, fewer physical symptoms, and lower levels of depression compared to those on chemotherapy. This data offers a meaningful glimpse into how patients experience therapy—an increasingly important part of how new treatments are assessed.

While these findings suggest a more manageable safety profile and lower healthcare burden, it's worth noting that longer-term safety data are still evolving, and tolerability may vary depending on patient comorbidities and local treatment protocols.

Overall, the PARADIGM trial didn't just show that azacitidine and venetoclax was comparable to intensive chemotherapy in eligible patients. This combination also appeared to offer meaningful advantages on several key measures—including event-free survival, response rates, early complications, hospitalization time, and early quality-of-life—in a population of induction-eligible adults.

Of course, overall survival data are still maturing. And as a phase 2 trial, PARADIGM sets the stage but doesn't close the case. We'll need larger studies to confirm these results. Still, for patients with higher-risk disease who might otherwise face a taxing inpatient course, these findings suggest a potentially less toxic and more efficient path to remission, and for many, a bridge to transplant.

In short, PARADIGM is challenging the long-standing paradigm that patient fitness determines the treatment intensity, and its related toxicity, that patients are exposed to. The trial suggests that high intensity doesn't always translate to better outcomes, and that lower-intensity approaches may deliver comparable or even superior efficacy, with fewer trade-offs in tolerability.

This has been an *AudioAbstract* for *Project Oncology*, and I'm Ryan Quigley. To hear this and other episodes in the series, visit ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.

Reference:

Fathi A, Perl A, Fell G, et al. Results from PARADIGM—a phase 2 randomized multi-center study comparing azacitidine and venetoclax to conventional induction chemotherapy for newly diagnosed fit adults with acute myeloid leukemia. Abstract #8236. Presented at: American Society of Hematology Annual Meeting; December 2025; San Diego, CA.