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Venetoclax plus azacitidine in younger adults with acute myeloid leukemia beyond historical comparisons. Comment on: "Venetoclax and azacitidine for younger acute myeloid leukemia patients independent of fitness for intensive chemotherapy"

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Xia Jiang: Conceptualization, investigation, writing – original draft, and writing – review and editing. Ying Lu: Conceptualization, supervision, validation, and writing – review and editing. Both authors approved the final manuscript and agree to be accountable for all aspects of the work.

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Conflict of interest

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To the Editor:

Watts and colleagues report a prospective pilot study of venetoclax plus azacitidine (VEN-AZA) in 36 adults aged 18-59 years with newly diagnosed, non-favorable-risk acute myeloid leukemia (AML). The overall response rate was 69%, 68% of responders achieved measurable residual disease negativity, and 53% proceeded to allogeneic stem cell transplantation (ASCT). In a post hoc 1:1 comparison with matched historical controls treated with intensive chemotherapy (IC), VEN-AZA was associated with higher response and ASCT rates, fewer inpatient days, lower transfusion and infectious burdens, and longer reported progression-free survival (PFS), without a significant overall-survival difference.¹ These prospective feasibility findings are clinically important, but the historical comparison supports a different and more limited level of causal inference.

Randomized evidence has emerged since enrollment in the pilot began. In the phase 2 PARADIGM trial, 172 induction-eligible adults were assigned to VEN-AZA or IC. Median event-free survival was 14.5 versus 6.2 months (hazard ratio, 0.57; 95% confidence interval, 0.39-0.84), with fewer grade 3 or higher infections and hemorrhagic events in the VEN-AZA group.² However, PARADIGM excluded core-binding-factor AML, FLT3-mutated disease, and NPM1-mutated disease in patients younger than 60 years, so its results apply to a selected population. A second randomized trial in 188 adults aged 18-59 years found venetoclax plus decitabine noninferior to idarubicin plus cytarabine for composite complete remission, with fewer severe infections; responders in both groups then received high-dose cytarabine consolidation.³ Together, these trials support integrating disease biology with physiologic fitness rather than treating fitness alone as the determinant of induction intensity. Regimens also differ: Watts *et al.* used venetoclax 600 mg for up to 28 days, whereas VIALE-A used 400 mg.⁴

The historical-control analysis should therefore be interpreted as supportive rather than confirmatory. Matching used only age within five years and European LeukemiaNet 2017 risk, while the median diagnosis year differed substantially between groups (2022 vs. 2017) and one third of controls lacked comprehensive genomic testing.¹ Supportive care, antifungal strategies, molecular classification, salvage treatment, donor access, and transplant selection changed during the 2013-2024 control period. Important covariates such as performance status, comorbidity, secondary AML, monocytic phenotype, molecular lesions, transplant intent, and center effects were not fully balanced. Standardized differences would describe baseline balance more appropriately than significance tests,⁵ and a target-trial framework could make eligibility,

treatment assignment, time zero, follow-up, outcomes, and estimands explicit.⁶ With only 36 matched pairs, extensive adjustment would be unstable; overlap, discordant pairs, absolute paired effects, and confidence intervals would be more informative.

Several reported endpoint and statistical details also merit clarification. The abstract gives median PFS as “not reached versus 60.8 months,” whereas Table 3 and the Results report 0 days for controls (95% confidence interval, 0-123 days).¹ Table 3 reports 19 complete remissions as 58%, although 19 of 36 is 53%. More importantly, nonresponders were assigned a PFS event on the date of diagnosis. Because 20 of 36 controls were refractory, a control median PFS of 0 is largely determined by this rule and resembles event-free or treatment-failure survival more than conventional PFS. A sensitivity analysis using a prespecified event-free survival definition would clarify robustness. The phrase that VEN-AZA was “at least as effective as IC” reads as a noninferiority conclusion, although the study was not randomized and no noninferiority margin was prespecified. Multiplicity also matters: numerous efficacy, resource-use, and subgroup comparisons were reported without an adjustment strategy, so P values should be treated as exploratory and accompanied by effect estimates and 95% confidence intervals. The stated “K analysis” requires clarification; if kappa was intended, it measures agreement rather than marginal differences. Methods and table footnotes should also identify the analysis used for each endpoint consistently.

ASCT is a post-baseline event rather than a simple binary outcome. A higher transplant proportion can reflect disease control, toxicity, referral practice, or calendar-era effects. Time to ASCT with death and refractory disease as competing events, or a multistate model spanning induction, remission, ASCT, relapse, and death, would better distinguish access to transplantation from post-transplant outcomes. Retrospective cohorts have reported broadly similar post-ASCT outcomes after VEN-AZA and IC,^{7,8} but analyses restricted to transplanted patients remain vulnerable to selection because patients must survive and respond sufficiently to undergo ASCT.

Finally, the biological subgroup findings are hypothesis-generating. European LeukemiaNet categories were developed mainly in intensively treated populations, and a pooled VEN-AZA analysis found limited discrimination with ELN 2017/2022 while proposing a four-gene classifier based on TP53, FLT3-ITD, NRAS, and KRAS.⁹ In the pilot, classifier groups contained only 23, nine, and four participants. Likewise, exclusion of monocytic AML after an interim response observation is biologically plausible because monocytic differentiation and

reduced BCL2 dependence are associated with venetoclax resistance,¹⁰ but results should be separated for patients enrolled before and after the amendment and externally validated.

Watts *et al.* provide useful prospective evidence that a transplant-oriented, lower-intensity strategy can achieve deep remissions with limited early resource use in selected non-favorable-risk AML. PARADIGM adds randomized support, but neither study resolves treatment choice for every induction-eligible molecular subgroup. Future comparisons should emphasize prespecified event-free survival, molecularly stratified treatment effects, and competing-risk or multistate analyses for transplantation, with effect sizes and uncertainty prioritized over isolated P-value thresholds. Claims of equivalence or superiority should remain limited to the populations and endpoints actually tested.

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