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Is CPX-351 the best path to remission for older patients with treatment-related or myelodysplastic-related acute myeloid leukemia?

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Editorial

Is CPX-351 the best path to remission for older patients with treatment-related or myelodysplastic-related acute myeloid leukemia?

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CPX-351, a liposomal formulation of daunorubicin and cytarabine, was approved by the FDA in 2017 for the treatment of newly-diagnosed acute myeloid leukemia (AML), with either myelodysplastic-related-changes (AML-MRC) or therapy-related (t-AML). Approval was based on the pivotal phase III study that randomized patients with t-AML/AML-MRC between the ages of 60 to 75 to CPX-351 versus standard "7+3" (daunorubicin and cytarabine), demonstrating improved overall survival (OS) with CPX-351 (median OS 9.5 versus 5.9 in the 7+3 arm).[1] Toxicity profiles were broadly comparable, and CPX-351 is now commonly offered to older patients with t-AML/AML-MRC instead of 7+3. The mechanism underlying its clinical advantage is unknown, but is thought to be related to enhanced marrow delivery and prolonged exposure.[2] Several limitations of the pivotal study have been raised, including the relatively low CR/CRi rate of 33.3% in the 7+3 control arm compared with historical benchmarks.

In this issue, Kotsos et al. [3] examine whether CPX-351 is also superior to a more intensive induction strategy than conventional 7+3. In a post-hoc analysis of three HOVON-SAAK-Nordic trials[4-6], the authors assembled a cohort of older adults with t-AML/AML-MRC who would have met eligibility criteria for the CPX-351 study. This cohort was derived from the control arms of these trials, in which patients received a 7+3-based induction, followed by an obligatory second cycle that included intermediate dose cytarabine (IDAC), plus/minus amsacrine. Outcomes from the 153 patients who received CPX-351 in the pivotal study were compared to 180 patients comprising the HOVON-SAAK-Nordic cohort. The effort is commendable and methodology meticulous. With all the caveats of inter-trial comparison notwithstanding, this analysis appears justified given similar eligibility criteria, contemporaneous study periods, and the conduct of all studies within large clinical trial frameworks. Nevertheless, the substantial differences in response rates across both control and experimental arms warrant cautious interpretation.

Results of this comparison demonstrate higher CR/CRi rates in the HOVON-SAAK-Nordic cohort compared to the CPX-351 group (67.8% versus 47.7%, $p<0.001$), an effect that was consistent across subgroups and age strata. Survival, however, was not significantly different, with a median OS of 10.1 months compared to 8.9, ($p=0.95$).

Notably, among patients who achieved CR/CRi and proceeded to allogeneic stem cell transplant (allo-HCT), OS was superior in the CPX-351 cohort (median OS not reached versus 14.4 months in the HOVON-SAAK-Nordic cohort, $p=0.007$, supplemental figure 4B). Rates of allo-HCT among responders were similar (54.1% versus 56.2%, $p=0.88$). However, given higher remission rates in the HOVON-SAAK-Nordic cohort, a greater proportion of their patients proceeded to transplant (36.6% versus 26.8% from the CPX-351 cohort), raising the possibility that patients from the CPX-351 cohort who ultimately underwent allo-HCT may represent a more favorable subset.

Returning to the question posed in our title, the analysis by Kotsos et al. suggests that induction intensification (double-induction + IDAC) improves remission rates compared to CPX-351. However, the absence of a corresponding OS advantage, despite higher response rates, and

similar transplant utilization, raises important questions. This discordance suggests that either CPX-351 confers advantages not fully understood, or that alternative strategies beyond induction intensification and improved CR/CRi rates are needed to improve long-term outcomes in this population.

One potential explanation for the improved post-transplant survival observed among the CPX-351 responders, is depth of remission. However, measurable residual disease (MRD) data are not available for either cohort, and there is no biologic rationale or data to suggest that CPX-351 would produce deeper responses than an intensified double-induction. Alternatively, CPX-351 patients may have reached transplant with less treatment-related toxicity. Only a minority of patients in the CPX-351 cohort received a second induction cycle, compared to the uniform double-induction approach in the HOVON-SAKK-Nordic cohort, which also included IDAC. Moreover, gastrointestinal toxicity may be less severe with CPX-351 compared to 7+3, although time to count recovery is longer with CPX-351.[7]

The question of whether all CRs are biologically equivalent continues to challenge the AML community. The success of the low intensity combination of hypomethylating agents with venetoclax (HMA/VEN) in inducing remission has further intensified this debate.[8] Conceptually, deeper remissions prior to allo-HCT may allow sufficient time for graft-versus-leukemia effects to develop, suggesting that the benefits of achieving a more profound, even if transient, response may be most relevant in patients who ultimately proceed to transplant. On the other hand, preservation of physiologic reserve prior to transplant is equally important, particularly in older adults. These competing priorities, depth of response versus treatment-related fitness, underscore the central tension in selecting induction strategies for this population. In this context, HMA/VEN as a potentially low toxicity remission-induction/post-remission/pre-transplant strategy, warrants further investigation.

This analysis leaves several key questions unresolved. In older patients with t-AML/AML-MRC, is CPX-351 superior not only to conventional 7+3 but also to intensified double-induction strategies? The present data suggest that the advantage may be confined to patients who proceed to allo-HCT. Conversely, the higher CR/CRi rates observed with intensified induction with IDAC, raise the possibility that such approaches may have a role in patients unlikely to undergo transplant. Whether elements of this strategy, such as intermediate-dose cytarabine, could be incorporated after lower-intensity regimens (e.g., after HMA/VEN) in non-transplant candidates also warrants investigation. Prospective studies, incorporating MRD assessments, will be critical to refining these approaches, and may differ across age groups. The current analysis suggests that intensified double-induction remains a potentially valuable strategy. Emphasis should be placed on attempting to go beyond remission, to strive to predict depth of response versus toxicity of each regimen.

Ultimately, in t-AML/AML-MRC, allo-HCT remains the most effective therapeutic modality. Induction therapy should therefore not be viewed in isolation, but as a means of delivering

patients to transplant in the best possible condition. The optimal regimen is not simply one that achieves remission, but that balances depth of response with tolerability, maximizing the likelihood that patients can successfully proceed to, and benefit from, transplant.

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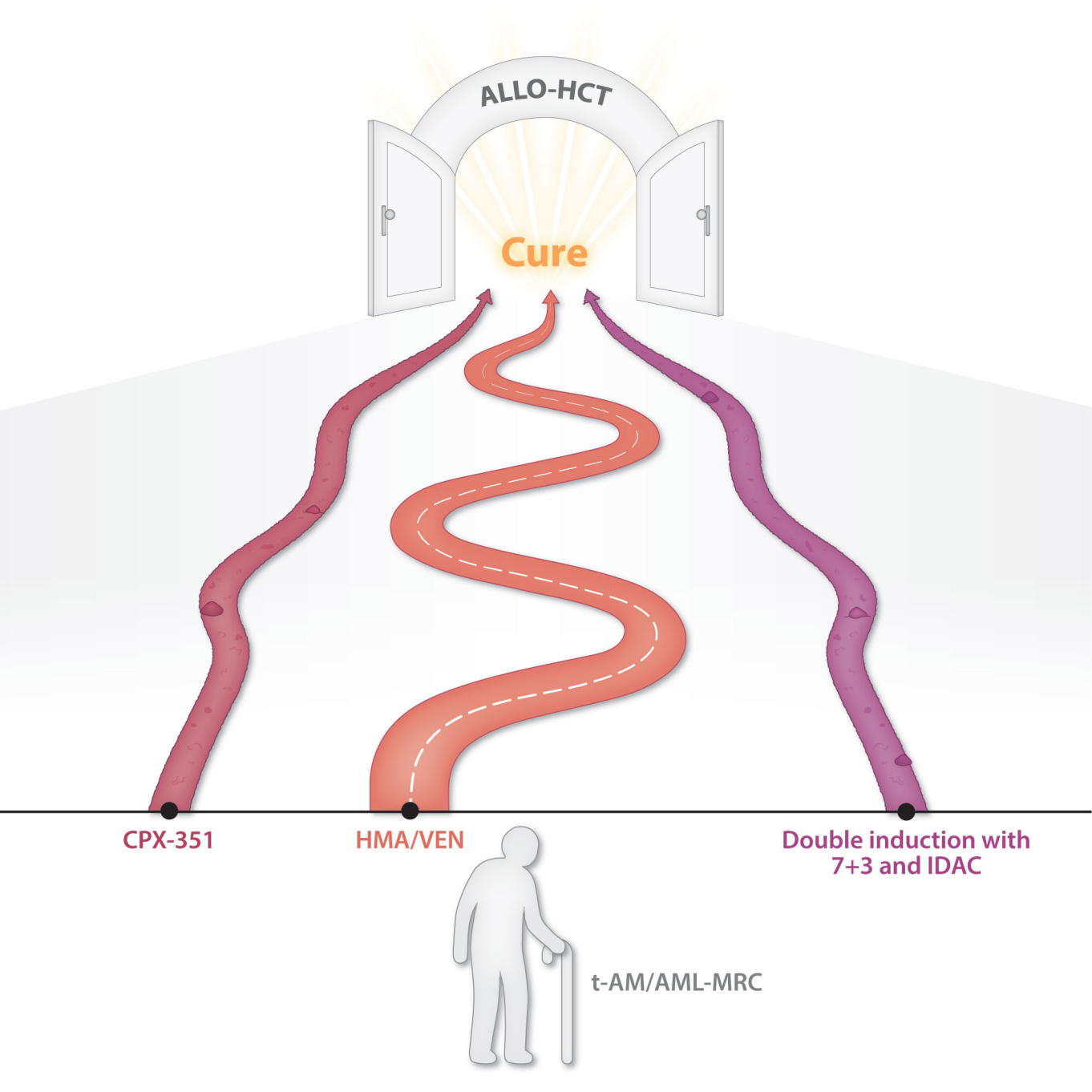
Figure legend:

Illustrative schema highlighting uncertainties in selecting induction strategies for achieving remission in older patients with t-AML/AML-MRC. Allogeneic hematopoietic stem cell transplantation (allo-HCT) represents the common therapeutic endpoint when cure is feasible. However, the optimal approach remains unclear (CPX-351 vs HMA/venetoclax vs standard 7+3, vs intensified double induction with intermediate-dose cytarabine), particularly with respect to balancing depth of remission and treatment-related toxicity.

Abbreviations: t-AML: treatment-related acute myeloid leukemia; AML-MRC: AML with myelodysplastic-related changes; allo-HCT: Allogeneic hematopoietic stem cell transplantation; HMA/VEN: hypomethylating agent / venetoclax; 7+3: standard anthracycline + cytarabine induction; IDAC: intermediate dose cytarabine


ALLO-HCT
Cure
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