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 Food and Drug Administration in 2017 for the treatment of newly-diagnosed acute myeloid leukemia (AML) with either myelodysplastic-related-changes (AML-MRC) or that is 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* the standard 7+3 regimen (daunorubicin and cytarabine), demonstrating improved overall survival (OS) with CPX-351 (median OS 9.5 *vs*. 5.9 months 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 the 7+3 regimen. 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 pointed out, including the relatively low complete response (CR)/complete response with incomplete hematologic recovery (CRi) rate of 33.3% in the 7+3 control arm compared with historical benchmarks.

In this issue of *Haematologica*, Kotsos *et al*.[3] examine whether CPX-351 is also superior to a more intensive induction strategy than the conventional 7+3 regimen. 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, the so-called HOVON-SAAK-Nordic 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) with or without amsacrine. Outcomes of the 153 patients who received CPX-351 in the pivotal study were compared to those of the 180 patients forming the HOVON-SAAK-Nordic cohort. The effort is commendable and methodology meticulous. Notwithstanding all the caveats of inter-trial comparisons, 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% *vs*. 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 in the HOVON-SAAK-Nordic cohort compared to 8.9 months in the CPX-351 group (*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 *vs*. 14.4 months in the HOVON-SAAK-Nordic cohort, *P*=0.007) (*Online Supplementary Figure S4B* of the paper by Kotsos *et al*.[3]). Rates of allo-HCT among responders were similar (54.1% in the HOVON-SAAK-Nordic cohort *vs*. 56.2% in the CPX-351 cohort, *P*=0.88). However, given higher remission rates in the HOVON-SAAK-Nordic cohort, a greater proportion of these patients proceeded to transplant (36.6% *vs*. 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

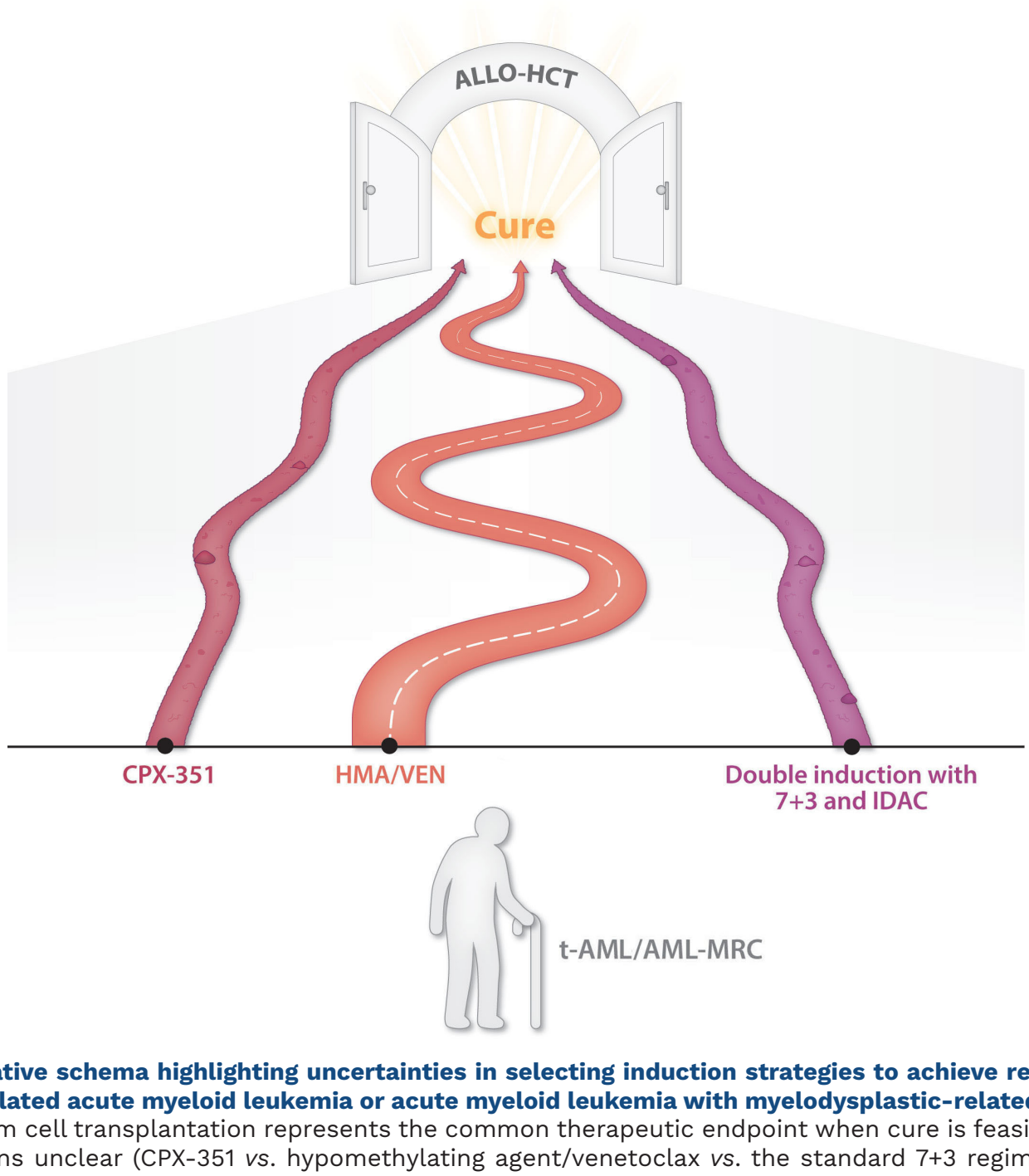


Figure 1. Illustrative schema highlighting uncertainties in selecting induction strategies to achieve remission in older patients with therapy-related acute myeloid leukemia or acute myeloid leukemia with myelodysplastic-related changes. Allogeneic hematopoietic stem cell transplantation represents the common therapeutic endpoint when cure is feasible. However, the optimal approach remains unclear (CPX-351 *vs*. hypomethylating agent/venetoclax *vs*. the standard 7+3 regimen *vs*. intensified double induction with intermediate-dose cytarabine), particularly with respect to balancing depth of remission and treatment-related toxicity. 7+3: standard anthracycline + cytarabine induction; ALLO-HCT: allogeneic hematopoietic stem cell transplantation; AML-MRC: acute myeloid leukemia with myelodysplastic-related changes; HMA/VEN: hypomethylating agent/venetoclax; IDAC: intermediate-dose cytarabine; t-AML: treatment-related acute myeloid leukemia.

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 biological 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 than with the 7+3 regimen, although time to blood count recovery is longer with CPX-351.[7]

The question of whether all CR 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 a physiological reserve prior to a 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-remis-

sion/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 the conventional 7+3 regimen 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 the IDAC, 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 (Figure 1). The optimal regimen is not simply one that achieves remission, but one that balances depth of response with tolerability, maximizing the likelihood that patients can successfully proceed to, and benefit from, a transplant.

Disclosures

MY-S has no conflicts of interest to disclose. YO reports advisory roles in Medison, Janssen, Astellas, BMS, and AbbVie and research funding from Minovia.

Contributions

MY-S and YO contributed equally to this editorial.

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