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Rethinking intensive salvage therapy in the venetoclax era

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Text:

Curative treatment for patients with relapsed or refractory acute myeloid leukemia (R/R AML) remains one of the greatest challenges in contemporary hematology. For medically fit patients, intensive salvage chemotherapy followed by allogeneic hematopoietic stem cell transplantation (alloHSCT) in remission has long been the only potentially curative strategy.[1] For this approach, effective salvage therapy with high remission rates is essential. Conventional regimens such as HAM, FLAG-IDA and MEC achieve complete remission rates of only ~50%, with median survival below one year. [1, 2] Therefore, re-induction regimens with higher efficacy are urgently needed.

In this issue of *Haematologica*, Berdel and colleagues[3] report the first large multicenter real-world analysis of high-dose cytarabine and mitoxantrone combined with venetoclax (HAM-VEN) in patients with R/R AML. Their study aimed to validate the findings of the recently published RELAX phase I/II trial (NCT04330820).[4] The RELAX trial demonstrated that HAM-VEN is a highly active salvage regimen, achieving a composite complete remission (CR/CRi) rate of 75% and enabling 88% of responders to proceed to alloHSCT.

The real-world analysis by Berdel et al. confirms these observations.[3] Despite including an older and clinically less favorable population with more prior venetoclax exposure, the authors report a CR/CRi rate of 69%, with 68% of patients proceeding to alloHSCT. Although cross-trial comparisons must be interpreted cautiously, these findings suggest that the efficacy of HAM-VEN extends beyond a highly selected clinical trial population. However, as a retrospective single-arm study, the analysis does not allow conclusions regarding comparative efficacy versus other salvage regimens.

In recent years, several biologically distinct strategies have emerged to bridge patients with R/R AML to alloHSCT. Venetoclax has improved remission rates across multiple intensive chemotherapy platforms, including FLAG-IDA, FLAI, CLIA, CPX-351 and HAM, while less-intensive venetoclax-based combinations have also shown meaningful activity and enabled a substantial proportion of patients to reach transplantation.[5-7] Targeted therapies further expand the therapeutic landscape, with FLT3 inhibitors such as gilteritinib and quizartinib demonstrating superior remission rates in FLT3-mutated AML.[8, 9] Together, these approaches represent remission-directed strategies aimed at achieving cytoreduction before alloHSCT. In parallel, sequential conditioning offers a conceptually different pathway: instead of pursuing deep remission prior to transplant, it focuses on disease control and early progression to alloHSCT. This strategy has shown non-inferiority to HAM-based re-induction and is associated with reduced early toxicity.[10]

With HAM-VEN, another effective re-induction regimen has been added to this expanding therapeutic landscape. Importantly, none of the non-transplanted patients in the current study

achieved durable survival, reinforcing that alloHSCT remains the cornerstone of curative therapy. Clinicians now face multiple viable pathways to bridge patients to alloHSCT, each with distinct efficacy, toxicity and applicability. The central challenge is therefore not identifying the single “best” regimen, but selecting the optimal route to transplantation for each individual patient.

What is ultimately needed is a framework that integrates patient fitness, disease biology, treatment history and molecular profile to guide selection of the optimal therapeutic pathway. Such a model should identify patients with highly proliferative disease who require urgent cytoreduction and are sufficiently fit to tolerate intensive chemotherapy, as well as those who may benefit more from targeted or venetoclax-based approaches. Patients with actionable mutations such as *NPM1*, *IDH1/2* or *FLT3* may be best served by molecularly targeted or less-intensive venetoclax-based combinations, particularly when fitness is limited or when disease biology predicts sensitivity to these agents. Conversely, patients with *TP53*-mutated disease or those previously treated with venetoclax, who have a high likelihood of refractoriness to re-induction, may be better suited for sequential conditioning strategies that prioritize disease control and early progression to alloHSCT rather than deep remission. However, these decisions also depend on donor availability and clinical dynamics, and sequential conditioning is not feasible in patients with progressive disease without an immediately available donor, who may therefore still require re-induction. Together, these considerations reflect the broader shift from treatment selection to patient selection, where the goal is not choosing the most potent regimen but determining the most appropriate route to alloHSCT for each individual patient.

Selecting the optimal pathway requires both accurate baseline characteristics and dynamic assessment of treatment response. Baseline clinical and molecular features guide initial therapy but are static and insufficient for subsequent decision making. In this context, measurable residual disease (MRD) represents an attractive biomarker, integrating the cumulative effects of leukemia biology, chemotherapy sensitivity, venetoclax susceptibility, immune-mediated clearance and microenvironmental interactions. MRD may help tailor transplant strategies by identifying patients who require additional disease control before transplantation or intensified post-transplant interventions.

Despite the high CR/CRi rate in the RELAX trial, only a minority of responding patients achieved MRD negativity. Although MRD results cannot be directly compared across studies due to methodological differences, these findings illustrate that the depth of remission varies substantially between regimens. While the value of MRD in the R/R setting is less well established, MRD positivity remains indicative of inferior treatment response and is likely associated with higher relapse risk post-transplant, warranting closer monitoring and consideration of additional therapeutic interventions. Whether achieving MRD negativity prior

to transplantation should be a therapeutic objective, or whether MRD is more valuable for post-transplant risk stratification and treatment adaptation, remains unresolved.

Berdel and colleagues demonstrate that HAM-VEN is reproducible outside a clinical trial setting and further support venetoclax as an important component of intensive salvage therapy.[3] The next challenge is not comparing salvage regimens, but integrating all available approaches to determine the optimal route to alloHSCT for each patient. This will require large datasets combining patient characteristics, treatment response and MRD to enable a more personalized decision-making framework. In this context, MRD should be regarded not only as a prognostic biomarker but as one component of a broader strategy guiding patient selection, transplant approaches and post-transplant management.

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