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by Xin Cai and Mingjun Kong

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Induction-response landmarks in salvage-free, transplantation-free survival for acute myeloid leukemia. Comment on: "Salvage-free, transplantation-free survival: a proposal for a new clinical endpoint in acute myeloid leukemia"

Xin Cai[1], Mingjun Kong[2*]

1. Guangzhou Medical University, Guangzhou, Guangdong, 511436, China

2. Peking University Third Hospital, Beijing, 100191, China

Corresponding author

Mingjun Kong, M.D.

Peking University Third Hospital

No. 49 Huayuan North Road, Haidian District

Beijing, 100191, China

E-mail: MJKongmed@163.com

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Récher and colleagues proposed salvage-free, transplantation-free survival (STFS) as a complementary endpoint for first-line therapy in acute myeloid leukemia (AML), supported by registry data and a reanalysis of a randomized trial.[1] They appropriately noted that counting transplantation as an event also reflects the treatment strategy. Another issue concerns the induction-response landmark and the clinical estimand: does the induction-failure component of STFS reflect nonresponse after the first cycle or failure of the protocol-defined induction strategy? Both may be informative, but they address different clinical questions.

STFS begins on day 1 of induction therapy and defines induction failure as failure to achieve complete remission (CR) or CR with incomplete hematologic recovery (CRi) after one cycle.[1] However, the DATAML cohort reported a CR/CRi rate of 83% after one or two cycles.[1] The 2022 European LeukemiaNet recommendations define refractory disease as failure to achieve remission by a prespecified response landmark (typically after two intensive induction courses) and likewise use a prespecified landmark for event-free survival (EFS) treatment failure.[2] These recommendations do not require STFS to use the same time points, nor should it be assumed that two cycles apply to all AML treatment regimens. The key question is whether the second planned induction course in the regimen is part of the first-line treatment strategy that STFS is intended to assess. A definition based on the first cycle focuses on early response, whereas a definition based on the treatment strategy assesses remission after completion of the planned induction courses.

The ALFA-0701 study illustrates this distinction. For patients with persistent blasts on

day 15 bone marrow examination, a second daunorubicin-cytarabine induction course was given, separate from subsequent salvage therapy.[3] Récher and colleagues reported 17 cases of induction failure in the gemtuzumab ozogamicin (GO) arm and 29 in the control arm (STFS Table 4).[1] These data are consistent with the investigator-assessed induction failure records in Lambert and colleagues' EFS Table 1,[3] although the populations analyzed differed (139 patients per arm in STFS, versus 135 and 136 in EFS). The earlier EFS report used CR or CRp (CR with incomplete platelet recovery) as the criterion, whereas STFS used the CR/CRi criterion. In addition, Lambert and colleagues reported 25 and 34 cases of induction failure after blinded independent review.[3] Differences in review methods do not indicate an error in STFS, but they highlight the importance of clearly defined classification rules. Were the induction failure cases in the STFS reanalysis re-evaluated at the individual patient level using the single-cycle CR/CRi definition, or were the original investigators' classifications directly adopted? The reported summary data do not allow this to be determined.

In a retrospective study of 302 patients, 58 required two cycles of intensive induction therapy to achieve remission, and their overall survival was worse than that of patients who achieved remission after the first cycle.[4] Delayed remission has prognostic significance but is not equivalent to persistent failure of the planned induction strategy. If a patient who responded in cycle 2 is subsequently classified as having experienced an STFS event after cycle 1, a later remission does not reverse that event. Under the strategy-based definition, the patient remains event-free unless another component of STFS occurs. Therefore, a drug that affects the timing of remission may influence the

induction-failure component of STFS without a corresponding effect on remission after planned induction therapy. This remains hypothetical, and no such bias has been demonstrated in the GO comparison.

Overall, STFS may be a useful complementary endpoint, but interpretation of its induction-failure component depends on the response landmark used. Reporting CR/CRi counts after one cycle and after protocol-planned reinduction, together with the classification of second-cycle responders and the dates assigned to induction-failure events, would clarify whether planned reinduction was considered continuation of first-line therapy or salvage. The handling of early deaths and unplanned salvage should also be specified. If individual-level data permit, a sensitivity analysis retaining induction day 1 as the time origin but assessing failure after completion of the protocol-defined induction strategy could compare induction-failure counts and timing, STFS curves, and GO-versus-control hazard ratios with 95% confidence intervals. Death, relapse, transplantation, and unplanned salvage should remain events under consistent rules. Such reporting would help distinguish early response from success of the planned induction strategy and support STFS as a complement to established AML endpoints.

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