Hematopoietic cell transplantation soon after first relapse in acute myeloid leukemia – the CONS

Yishai Ofran[1] and Jacob M. Rowe[1,2,3]

[1]1Hematology and Stem Cell Transplantation Department and the Eisenberg R&D Authority, Shaare Zedek Medical Center, Hebrew University Jerusalem, Jerusalem; [2]Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa and [3]The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel

Correspondence: Y. Ofran
yofran@szmc.org.il

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"Happy families are all alike; every unhappy family is unhappy in its own way" – Leo Tolstoy

Adapting the opening line of Tolstoy's "Anna Karenina", we could say: "Patients with acute myeloid leukemia (AML) achieving long-lasting remission are all alike; but each patient with relapsed / refractory disease progresses in their own unique way". In the past, given the devastating outcome and the limited therapeutic options available, clinical trials were designed to focus on relapsed or refractory disease, leaving little space to consider the heterogeneity in molecular profile, timing of relapse, and intensity and type of therapy that yielded first remission. For relapsed or refractory patients transplanted while not in remission, historic survival data from 30 years ago were devastating, with only 25% overall survival.[1,2] These results led to a longstanding standard approach that mandates attempts to achieve a second remission, or maximal response, prior to a transplant.

This paradigm was challenged by a recent randomized study.[3] In the German ETAL-3-ASAP trial, patients were randomized to receive reinduction (salvage) chemotherapy (based on high-dose cytarabine) prior to personalized conditioning regimen *versus* immediate allogeneic hematopoietic stem cell transplant (alloHSCT) using a FLAMSA-RIC sequential regimen consisting of intensive chemotherapy (including cytarabine) followed by a reduced-intensity conditioning.[4,5] Although the predefined cutoff for non-inferiority of immediate transplantation had not been achieved in this trial, the almost identical outcome of the two arms leaves room for adopting an immediate transplantation approach.

Copelan and Gale argue for implementing immediate transplantation as a new standard.[6] They correctly note that current practice is not evidence-based, if one adheres to the requirement for large prospective randomized studies. It is, however, based on a sound scientific rationale and substantial supporting observational and retrospective data. Such a course is not without risks, not least for increasing toxicities of the transplant, particularly if a significant response was not achieved. It seems that the data from the ASAP trial do not dismiss this risk. Furthermore, the high rates of actual transplants in both arms (96% in the disease control group *vs*. 93% in the remission induction group) are quite exceptional in an intention-to-treat trial, suggesting patient selection for either an immediately available donor (unlikely, since only 15% had matched sibling donors) or an indolent disease biology that allowed waiting for a transplant. The reported data from the ASAP trial reflect recent improvements in transplantation and the development of sequential protocols. Moreover, current treatment options for a patient with AML at relapse are not binary, being a choice between intensive chemotherapy alone or immediate transplantation. The intensive salvage approach used in the ASAP trial, with mitoxantrone and cytarabine (HAM), has been used for more than 30 years. Disappointingly, the rate of reported remissions after the HAM regimen has only marginally increased from 44-53% during the 1990s[7-9] to the current 51-58%.[10,11]

One cannot discount the importance of reaching minimal residual disease (MRD) prior to an alloHSCT,[12-15] which has been reported in multiple studies and consensus reports.[16-21] This is not surprising and is in line with the concept applicable to all immunotherapies. The FLAMSA-RIC regimen used in the ASAP trial includes remission-inducing chemotherapy prior to the conditioning (RIC) such that it is likely that the aim of reaching MRD was also achieved in a substantial number of patients, although this was not documented. In similar regimens, a reduction in the post-alloHSCT relapse rate was shown to be associated with peripheral blast clearance after induction.[22]

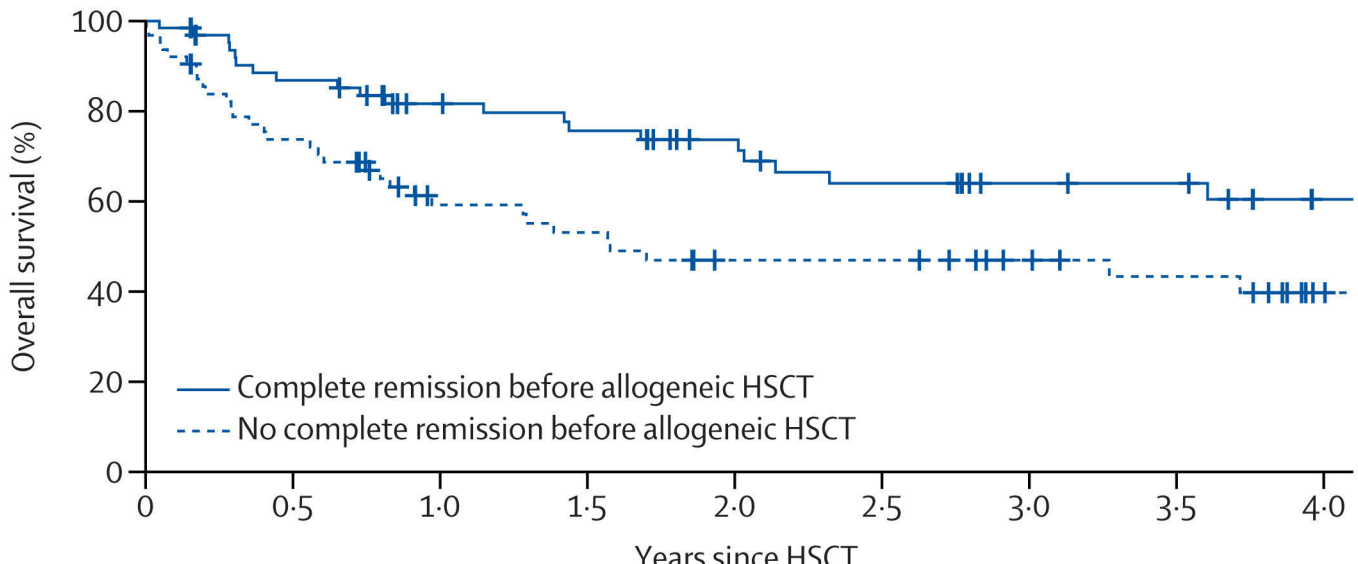
For the entire population of induction failure or relapsed AML, a cogent argument must be made for a more personalized approach. Twenty years ago, Sing and Lipton[23] suggested that, in select patients, alloHSCT may be offered to relapsed patients, even if not in remission, based on

fitness (young age, absence of comorbidities) and favorable prognostic factors (such as early relapse and cytogenetics). The rationale behind their suggestion was to minimize the risk of transplant-related mortality by offering immediate transplantation to those who are more likely to survive the transplantation despite active disease. Over the past 25 years, transplantation protocols and outcome have significantly improved. The ASAP protocol was designed with confidence in the ability of most patients to undergo a transplant, and thus for the salvage chemotherapy approach. An alloHSCT was considered even if re-induction failed, and a significant proportion of such patients were eventually transplanted with active leukemia. Immediate transplantation was conducted using a sequential (FLAM-SA-like) protocol, which includes an intensive induction for all patients in this arm, and this was shown to be associated with a low rate of treatment-related mortality.

Today, in 2025, transplantation should be viewed as a target for most patients with relapsed or refractory disease. However, one cannot dispute the fact that the results of alloSCT are better when conducted with minimal disease burden. Indeed, in the ASAP induction arm, outcome for those who achieved remission prior to transplantation was significantly better than those who failed induction (Figure 1). As a practical suggestion, it seems that, instead of choosing a uniform approach with immediate transplantation for all, efforts should be directed towards better induction regimens that may lead to higher rates of deep responses prior to transplantation and, for some patients, sparing the need for a transplant. The response to reinduction therapy can be crucial for prognosis and therapy, helping to determine who should continue to transplant, who may not need a transplant, and in whom a transplant may be futile (Figure 2). By administering induction upfront, one can obtain MRD status prior to transplantation and offer myeloablative conditioning to those who may benefit from it.[24] Unlike the strategy suggested by Copelan and Gale of immediate transplantation as a new standard of care (supported by one randomized study, as above), and by Sing and Lipton who emphasized minimizing transplant-related mortality, the focus should be the opposite: saving immediate transplantation for those who are less likely to achieve a quality response to intensive salvage.

Recent studies suggest that adding ventoclax to intensive salvage may significantly improve the complete remission (CR) rate.[25,26] Focusing on induction as a potential beneficial step towards successful transplantation leads to selecting the best available induction regimen. Incorporating ventoclax, or any relevant targeted drug, is likely to increase the proportion of patients undergoing transplantation in optimal conditions. For example, on the one hand, patients who are highly likely to respond to a FLAG-Ida regimen[27] (e.g., late relapses, favorable cytogenetics in fit and young patients) should be encouraged to receive this intensive reinduction regimen while, at the other end of the spectrum, patients who may not be able to tolerate very intensive salvage or prolonged neutropenia may, indeed, be candidates for immediate transplantation.

The issue of immediate *versus* late transplantation relates to patients with morphological evidence of disease. Howev-



Number at risk (number censored)									
Complete remission	65	52	42	38	31	26	20	19	11
	(0)	(5)	(12)	(13)	(19)	(20)	(26)	(27)	(34)
No complete remission	63	44	29	26	20	20	15	12	4
	(0)	(3)	(10)	(10)	(13)	(13)	(18)	(20)	(27)

Figure 1. Overall survival after allogeneic hematopoietic stem cell transplantation by measures for the disease control group and by response to salvage chemotherapy. Reproduced from Stelljes *et al.*,[3] with permission. HSCT: hematopoietic stem cell transplantation.

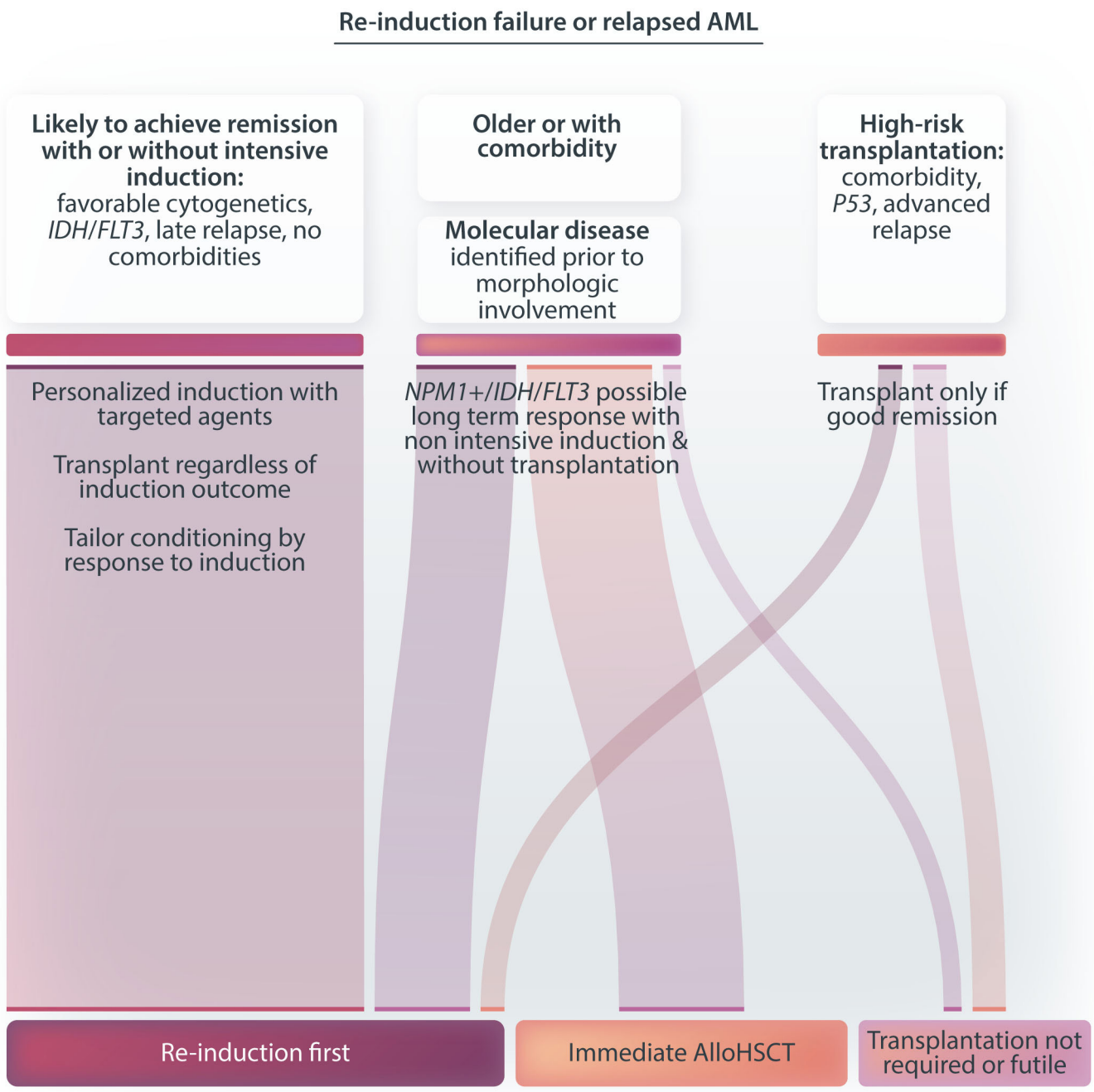


Figure 2. An abbreviated personalized therapeutic algorithm for patients with acute myeloid leukemia who failed induction or relapsed. AML: acute myeloid leukemia; AlloHSCT: allogeneic hematopoietic stem cell transplantation.

er, additional consideration is needed for those presenting with molecular relapse. Robust data regarding treatment of molecular relapses are available for patients who are *NPM1*-positive showing promising results with non-intensive regimens, and even with no transplantation.[28-30]

While prospective randomized studies are crucial, they are difficult to conduct given the narrow window of eligible patients, i.e., those with immediate donor availability, typically matched sibling donors. In the absence of definitive prospective studies, the current practice of treating relapsed patients with chemotherapy pre-transplant remains, with notable exceptions, a reasonable standard based on a sound rationale and supported by a multitude of retrospective studies.

Disclosures

No conflicts of interest to disclose.

Contributions

Both authors contributed equally.

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