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by Xavier Calvo

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Acute myeloid leukemia at first relapse: approaching the precipice

Xavier Calvo¹.

¹Laboratori de Citologia Hematològica, Servei de Patologia, Hospital del Mar, Grup de Recerca Translacional en Neoplaàsies Hematològiques (GRETNHE), Hospital del Mar Research Institute (IMIM), Barcelona, Spain.

Corresponding author: Xavier Calvo, Hospital del Mar, Paseo Marítimo, 25, 08003 Barcelona, Spain; e-mail: xcalvo@psmar.cat

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ORCID: https://orcid.org/0000-0001-7934-9130
In this issue of *Haematologica*, Bataller et al. present an interesting study that explores the outcomes and genetic dynamics of acute myeloid leukemia (AML) at first relapse (AMLr). The authors conducted a comprehensive analysis of 875 patients who were newly diagnosed with AML and received both intensive treatment (IT) and low-intensity therapies (LIT). After a median follow-up of 25 months, relapse was observed in 197 patients who had achieved a complete response (CR), representing 31% of the 637 patients with CR (Figure 1). The heterogeneity of the cohort impedes the ability to draw definitive prognostic conclusions for specific subgroups of AMLr, such as those with core-binding factor AML. This subgroup, particularly in the case of AML with CBFB::MYH11 rearrangement, has demonstrated a more favorable prognosis within AMLr in previous studies. In this context, it is pertinent to note that the 2022 ELN risk classification did not allow for discrimination of AMLr prognosis in this series. However, the study is invaluable in elucidating the overall poor prognosis of AMLr treated in a highly specialized center with access to a broad spectrum of novel therapies, such as FLT3 inhibitors, IDH1/IDH2 inhibitors, venetoclax, and checkpoint inhibitors (Figure 1).

Likewise, the inclusion of both young and older patients provides a prognosis analysis that is free from the biases commonly seen in previous studies focusing predominantly on younger patients receiving intensive treatment. Consequently, the data derived from the study by Bataller et al. constitute an excellent source of real-world evidence. Analysis of the data reveals disheartening outcomes: the median overall survival (mOS) for AMLr is 5.3 months, with only 17.6% and 7.3% of patients surviving beyond one and two years, respectively. The overall response rate remains low irrespective of the treatment intensity (38% for IT vs. 35% for LIT), and no notable differences in overall survival (OS) were noted between the IT and LIT cohorts (mOS: 6.6 months for IT vs. 4.9 months for LIT) (Figure 1). Furthermore, only 10% of patients experiencing relapse were eligible for either a first or second allogeneic hematopoietic stem cell transplant. Despite the bleak scenario, the authors identified four independent prognostic factors for OS in AMLr: white blood cell count greater than 20 x 10^9/L, a duration of less than 12 months from CR to relapse, adverse cytogenetics (including complex/monosomal karyotype, alterations of chromosome 5 and/or chromosome 7), and KMT2A rearrangements (Figure 1). Based on these factors, they developed a prognostic scoring system (0-1 vs. 2 or more variables). While inherent biases due to overfitting are unavoidable when comparing prognostic scores derived from one's own data with pre-existing indices, the new score appears to offer a slight increase in predictive accuracy. However, it is important to note that all scores demonstrate limited predictive power. Notably, the demographic and treatment characteristics of this cohort, encompassing both young and elderly patients undergoing IT and LIT, markedly differ from those in most series that informed prior prognostic models, which predominantly included younger patients receiving IT.

Despite the aforementioned modest enhancement in accuracy, it is worth noting that the prognosis of patients in the best and worst possible scenarios shows minimal variance and is uniformly poor. The authors present an interesting analysis of ‘adjusted survival curves’ within the framework of their Cox regression analysis, allowing for the assessment of patient survival based on the presence of individual score items, in contrast to those lacking such factors, with adjustments made for the remaining variables of the Cox model. For example, utilizing this methodology, the mOS for patients with adverse cytogenetics compared to those without indicates a consistently dismal prognosis in both groups (4.2 vs. 6.7 months, respectively).

Another remarkable contribution of the article by Bataller et al. is a thorough analysis of the genetic dynamics of relapse, a subject not extensively covered in existing literature, particularly in such large series. For 164 of the 197 patients with AMLr, paired genetic data
from diagnosis and relapse were available. The study introduces innovative analytical concepts, specifically the emergence and clearance rates, to facilitate a comprehensive understanding of the data. The genetic profiles at diagnosis were compared with those at relapse for both the entire cohort and the AMLr subset. Additionally, the genomic landscape at diagnosis for all patients was analyzed against those who later relapsed, to identify potential genomic predictors of relapse. Notably, at relapse, mutations in genes involved in pathway signaling frequently diminished (i.e., FLT3, KIT, NF1), whereas clonal founding mutations or those associated with clonal hematopoiesis (i.e., TET2, ASXL1, DNMT3A, SRSF2), alongside TP53, were more likely to persist (Figure 1). Furthermore, patients who received IT showed a higher emergence rate of TP53 mutations, aligning with findings from previous studies\(^\text{10}\). Another notable finding is that patients with a normal karyotype tended to acquire cytogenetic alterations at relapse, especially adverse cytogenetics. The emergence of complex karyotypes with alterations in chromosomes 5 and 7 raises the question of whether these cases might represent therapy-related AML (t-AML) rather than AMLr. The small sample size of patients with these characteristics limited the exploration of this hypothesis, although it is noteworthy that the latency periods between CR and relapse were more consistent with AMLr than with t-AML. Finally, the sub-study on patients treated with FLT3 inhibitors is particularly interesting.

In conclusion, two reflections come to mind. The first consideration is that, given the dire nature of the scenario, it is imperative to expedite the translation of research findings from bench to bedside with the utmost urgency. In this regard, studies such as that by Bataller et al.\(^1\) are much needed to provide us with a clear picture of where we stand and the long road ahead. The second reflection is that, considering the dismal prognosis of AMLr, current efforts should be directed towards improving the depth of complete responses in frontline and maintenance therapies to prevent reaching the point of no return that AMLr currently represents.


Figure 1. Sankey diagram of 875 patients diagnosed with AML who received induction therapy. Demographic data, 2022 ELN risk classification, and treatments received are collected for all patients with AML at diagnosis and for patients with AML at first relapse. Additionally, outcome data and genetic dynamics of patients with AML at first relapse are presented. AML: acute myeloid leukemia, ELN: European LeukemiaNet, IT: intensive treatment, LIT: low-intensity therapies, FLT3i: FLT3 inhibitors, IDH1/2i: IDH1/2 inhibitors, GO: Gemtuzumab Ozogamicin, OS: overall survival, ORR: overall response rate, CR: complete response, CRi: CR with incomplete hematologic recovery, TRM: transplant-related mortality.
Median age: 67 (21-95 years)
24 (15%) 2022 ELN favorable
26 (14%) 2022 ELN intermediate
110 (67%) 2022 ELN adverse

32 (20%) IT (9 (28%), venetoclax)
132 (80%) LIT (68 (52%), venetoclax)
18 (11%) FLT3i
18 (11%) IDH1/2i
12 (7%) GO
33 (20%) Non-GO AML-directed immunotherapy

Median OS: 5.3 months
1-year OS: 17.6%
2-year OS: 7.3%

ORR and median OS
IT: 38% (6.6 months)
LIT: 35% (4.9 months)

Independent prognostic factors for OS
WBC > 20 x 10^9/L
CR to relapse < 12 months
Adverse cytogenetics
KMT2A rearrangements

Genetic dynamics of relapse
Signaling pathway mutations (i.e. FLT3-ITD, FLT3-TKD, NF1, KIT) showed a higher clearance rate
CH-related (i.e. DNMT3A, TET2, SRSF2) and TP53 mutations showed a lower clearance rate

Median age: 65 (18-94 years)
175 (21%) 2022 ELN favorable
199 (24%) 2022 ELN intermediate
470 (56%) 2022 ELN adverse

348 (40%) IT (144 (41%), venetoclax)
527 (60%) LIT (379 (72%), venetoclax)
101 (12%) FLT3i
22 (3%) IDH1/2i
62 (7%) GO
74 (9%) Checkpoint inhibitors