Acute myeloid leukemia at first relapse: approaching the precipice

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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).[1] The authors conducted a comprehensive analysis of 875 patients who were newly diagnosed with AML and received intensive treatment or low-intensity therapies. After a median follow-up of 25 months, relapse was observed in 197 patients who had achieved a complete response, representing 31% of the 637 patients with a complete response (Figure 1). The heterogeneity of the cohort prevents definitive prognostic conclusions being drawn 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.[2-4] In this context, it is pertinent to note that the 2022 European LeukemiaNet risk classification did not enable 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 enables an analysis of prognosis that is free from the biases commonly seen in previous studies focusing predominantly on younger patients receiving intensive treatment.[2,4-7] Consequently, the data derived from the study by Bataller *et al.*[1] constitute an excellent source of real-world evidence.

Analysis of the data reveals disheartening outcomes: the median overall survival for subjects with AMLr was 5.3 months, with only 17.6% and 7.3% of patients surviving beyond 1 and 2 years, respectively. The overall response rate remained low irrespective of the treatment intensity (38% for intensive treatment *vs*. 35% for low-intensity therapies), and no notable differences in overall survival were noted between the cohorts managed with intensive treatment or low-intensity therapies (median overall survival: 6.6 months for intensive treatment *vs*. 4.9 months for low-intensity therapies) (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 overall survival in AMLr: white blood cell count greater than $20x10^9$/L, a duration period of less than 12 months from complete response 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.[1,2,4,6,7] 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 intensive treatment and low-intensity therapies, differ markedly from those in most series that informed prior prognostic models, which predominantly included younger patients receiving intensive treatment.[2,4-7] 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 patients' 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 median overall survival for patients with adverse cytogenetics compared to those

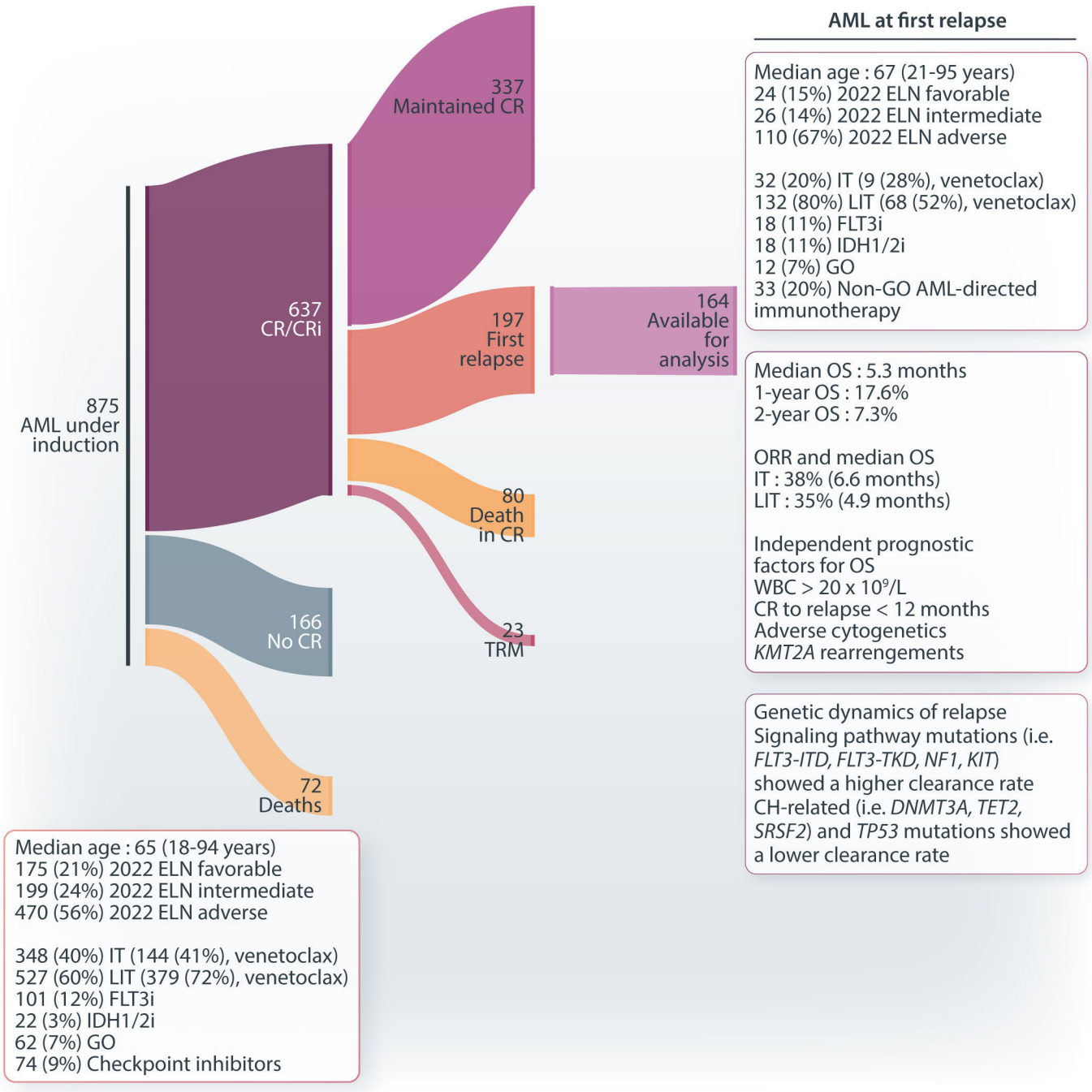

Figure 1. Sankey diagram of 875 patients diagnosed with acute myeloid leukemia who received induction therapy. Demographic data, 2022 European LeukemiaNet risk classification, and treatments received are provided for all patients with acute myeloid leukemia (AML) at diagnosis and for patients with AML at first relapse. Additionally, outcome data and genetic dynamics of patients with AML at first relapse are presented. CR: complete response; CRi: CR with incomplete hematologic recovery; ELN: European LeukemiaNet; IT: intensive treatment; LIT: low-intensity therapies; FLT3i: FLT3 inhibitors; IDH1/2i: IDH1/2 inhibitors; GO: gemtuzumab ozogamicin; TRM: transplant-related mortality; OS: overall survival; ORR: overall response rate; WBC: white blood cell count; CH: clonal hematopoiesis.

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.*[1] is a thorough analysis of the genetic dynamics of relapse, a subject not extensively covered in existing literature, particularly in such large series.[8,9] 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 that of the patients 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 intensive treatment showed a higher emergence rate of *TP53* mutations, aligning with findings from previous studies.[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 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 complete response and relapse were more consistent with AMLr than with therapy-related 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 to frontline and maintenance therapies to prevent reaching the point of no return that AMLr currently represents.

Disclosures

No conflicts of interest to disclose.

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