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Surveying survival: benchmarking acute myeloid leukemia outcomes without transplant

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The early 1800s saw the first recorded use of the benchmark, a chiseled fissure into which land surveyors could insert a “bench” to rest a leveling iron and consistently confirm a feature’s relation to mean sea level and other fixed points for map making. Just as rising sea level and topographical changes can progressively antiquate the precision of fixed surveying benchmarks, decades of advances in the management of acute myeloid leukemia (AML) have translated into progressive improvement in relapse-free survival (RFS) and overall survival (OS) of patients with the disease. Much of the improvement has been ascribed to the development of more efficacious AML-directed therapy, better supportive care, but also greater donor availability for and reduction of mortality related to allogeneic hematopoietic stem cell transplantation (alloHCT) for patients in first remission (CR1). Relatively favorable disease biology and, conversely, poor candidacy limit alloHCT in CR1 to a minority of patients. Given its relevance, contemporary benchmarks of survival for patients in CR1 not proceeding to alloHCT are needed.

The current issue of *Haematologica* provides this insight in which Kugler and colleagues report their single-center, retrospective analysis of 362 patients treated for newly diagnosed, non-core binding factor, “*de novo*” AML between 2016-2023, achieving CR1, and not consolidated with alloHCT.[1] Variance in both disease, treatment and response characteristics begets variance in event-based outcomes and thus how many and where benchmarks should be placed. The rate of European LeukemiaNet (ELN) 2022 favorable risk disease was similar (25 vs 20%), although a doubled rate of intermediate risk disease (43% vs 20%) was observed between patents who received intensive therapy (IT) and less-intensive therapy (LIT), respectively. Attention is paid to the 105 (40.9%) patents who received IT with approximately half also receiving it in combination with currently off-label venetoclax. Amongst patients treated with LIT, there was an enrichment for myelodysplasia-related lesions and approximately three-quarters received venetoclax with remaining patients being treated largely in the pre-venetoclax era, despite half qualified as having ELN 2024 favorable risk or predicted venetoclax-susceptible disease. Most patients were treated on a clinical trial.

In surveying several subgroups, we can trace several edifying benchmarks. Amongst patients achieving CR1 after IT, median RFS and OS was 20.9 months and 27 months, respectively, with the addition of venetoclax neither increasing the rate of multiparameter flow cytometric analysis (MFC)-measurable residual disease (MRD)-negativity (assessed locally with a sensitivity of 10^{-4} at the time of best response) nor RFS/OS estimates in this population.

Furthermore, albeit not reaching a statistically significant difference, ELN 2022 favorable and intermediate risk disease associated with an RFS of 58 and 25.5 months, respectively. The median RFS and OS for patients treated with venetoclax-inclusive LIT was 10.8 and 16.6 months, respectively, approximating estimates from VIALE-A.[2] In line with prior data,[3] better RFS (12.2 vs 5.9 months, p<0.01) and OS (18.8 vs 13.5 months, p=0.01) were observed amongst the 55.6% of patients achieving MFC-MRD-negativity with LIT.

Of particular interest are patients with "intermediate" risk disease, for which the definition evolves and with it an appraisal of whether alloHCT in CR1 is wise. The offered ~40% rate of 2-year LFS for patients with intermediate risk AML after IT and not proceeding to alloHCT in CR1 aligns with historical United Kingdom Medical Research Council (MRC) data and that from randomized trial data, although differing in their molecular-devoid definition of "intermediate" risk disease.[4,5] The value of MFC-MRD-negativity, previously shown to have significant impact on survival in both IT and LIT-treated populations,[3,6] in ELN 2022 intermediate risk disease was limited in the current study, but may predict similar OS irrespective of consolidative alloHCT.[7] The true benefit of CR1 alloHCT in this population requires further study in the era of molecular and MRD-adapted risk assignment, and may be elucidated by future randomized data (e.g. RESOLVE trial). Focus is also due on patients with *NPM1*-mutated AML, who when achieving qPCR *NPM1* MRD-negativity after first IC consolidation do not appear to benefit from alloHCT in CR1.[8] Co-mutation with secondary ontogeny lesions do not yet alter this subset's ELN favorable risk assignment, although some data challenge this position with RFS/OS approximating that expected with intermediate risk disease. Kugler and colleagues found no difference in RFS/OS in the overall and LIT cohorts (IT subgroup analysis limited by numbers).

Several considerations should before heeded while adopting these benchmarks to help physicians and patients alike map expectations and/or navigate a decision to proceed to alloHCT in CR1. It is only fitting that these benchmark estimates derive from a landmarked analysis, which although appropriate given the research question, already selects for disease biology likely favorable beyond that captured. It also makes uncertain why patients pre-IT were considered candidates or had sufficient access to also receive venetoclax, either on trial or commercially off-label. Although the emerging data for integrating venetoclax into frontline IT are encouraging,[9,10] randomized data are needed to confirm the true benefits. The authors also volunteer the lack of accounting for why patients, including the 105 patients with majority having ELN 2022 intermediate/adverse risk disease, who achieved post-IT CR1, but did not proceed to

potentially curative alloHCT. The influence of other events on RFS estimates, such as LIT maintenance therapy after completion of IT consolidation (received by one-quarter of patients completing IT chemo-consolidation, per author communication) or MRD re-emergence (which was not qualified as a relapse event). Increasing understanding and capture of molecular MRD, shown significant ability to discriminate outcomes after IT and LIT, particularly for patients faced with *NPM1*- and/or *FLT3*-ITD-mutated disease, will further refine benchmark placement.

Despite being derived from - and perhaps limiting externally validity outside another - large tertiary center with broad access to novel agents and clinical trials, the benchmarks offered by Kugler *et al* are contemporary and informative. CR1 duration(s) without alloHCT are expected to continually extend with novel therapies, optimized MRD platforms and well-designed studies of how to use them. Systematically surveying the terrain of RFS, in parallel, to accurately place and raise benchmarks may ensure that each generation of patients stands on firmer, higher ground than the last.

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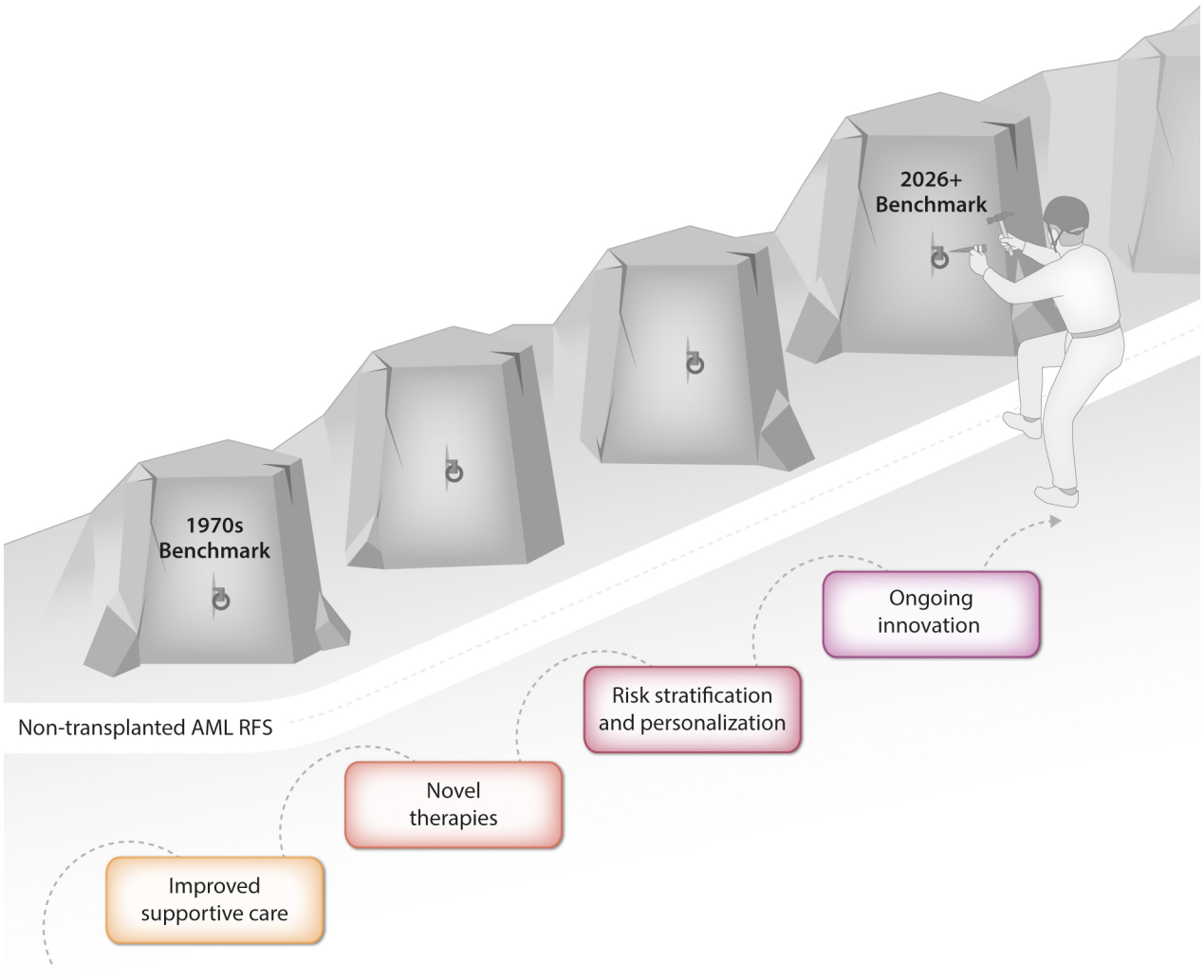
Figure 1. Rising elevations in acute myeloid leukemia relapse-free survival benchmarks without transplant. AML, acute myeloid leukemia; RFS, relapse-free survival.


1970s
Benchmark
2026+
Benchmark
Non-transplanted AML RFS
Improved
supportive care
Novel
therapies
Risk stratification
and personalization
Ongoing
innovation