We still need to hit hard in acute myeloid leukemia, but only in the right patients

Arnold Ganser

Hannover Medical School, Hannover, Germany

Correspondence: A. Ganser
ganser.arnold@mh-hannover.de

Received: December 2, 2024.
Accepted: December 30, 2024.
Early view: January 9, 2025.

https://doi.org/10.3324/haematol.2024.286822

In the present issue of *Haematologica*, Sobas *et al*. present the findings of the pan-European dataset of the HARMO-NY Alliance on the improvements of treatment outcome in a large cohort (N=5,359) of adult patients (age range, 15-86 years) with acute myeloid leukemia (AML) treated with intensive chemotherapy ("3+7" backbone) followed by consolidation therapy with high-dose cytosine-arabinoside or allogeneic hematopoietic cell transplantation (allo-HCT) over two decades from 1997-2016.[1] Patients with acute promyelocytic leukemia, mixed-lineage AML, and AML of ambiguous lineage were excluded. The distribution of patients according to European LeukemiaNet (ELN) 2017 risk categories was comparable in four, roughly equally sized cohorts divided according to time period of diagnosis (Table 1).[2] None of the patients received targeted therapy. The median overall survival increased significantly from 15.5 months to 37.8 months. While the complete remission rate remained unchanged over the different time periods, the 30-day and 60-day mortality improved significantly (Table 1). In ELN favorable- and intermediate-risk groups, overall survival only improved over time in the non-transplanted patients, while in the high-risk group both non-transplanted and transplanted patients showed improved survival.

Why are these data interesting in a time in which targeted drugs such as FLT3 inhibitors and – to a lesser degree – IDH1/2 inhibitors have become standard additions to the "3+7" induction protocols and in which elderly and unfit patients are regularly treated with hypomethylating agents and venetoclax?[3] Although previous publications have demonstrated improvement in treatment outcomes over time,[4] the data presented by Sobas *et al*. come from patients treated in prospective clinical trials and the re-

Table 1. Characteristics of the cohorts of patients with acute myeloid leukemia according to time periods of diagnosis.

Characteristics	1997-2002 N=1,127	2002-2006 N=1,294	2007-2011 N=1,821	2012-2016 N=1,117
Age in years				
Median	55	51	53	55
Range	17-84	15-85	16-86	17-85
Female, %	45.2	47.9	46.8	46.2
ELN 2017 risk category, %				
Favorable	33.3	28.2	29.5	28
Intermediate	35.3	37.4	33	27.5
Adverse	31.3	34.4	37.5	44.5
Intensive regimens, %				
<70 years	88.4	94.2	94.1	93.5
≥70 years	11.6	5.8	5.9	6.5
Early death, %				
≤30 days	6.3	4.4	4.17	2.5
≤60 days	13.05	8.11	7.14	4.74

ELN: European LeukemiaNet.

al-world setting outside trials in more than 100 leukemia treatment centers and are, therefore, representative. Since the induction therapy was similar in the centers, the decrease in early mortality from 13% in the first treatment period to 4.7% in the last indicates better supportive care and greater experience with high-dose cytarabine since the publication describing its use by Mayer *et al*. in 1994,[5] broader use of anti-infective agents including antifungals,[6] easier access to intensive care units,[7] and probably treatment in specialized leukemia treatment centers. In addition, the data clearly show that allogeneic stem cell transplantation is the most important curative consolidation therapy for both younger and older patients in the ELN 2017 high-risk group.[2] While it is conceivable that in ELN 2017 low-risk patients allo-HCT in first complete remission did not improve overall survival, the results in the intermediate-risk group, which show some fluctuation in the fraction of patients going on to allo-HCT, might reflect the change in patient selection occurring after publication of the seminal paper by Schlenk *et al*. in 2008 which indicated that *FLT3*-mutated AML patients should be transplanted in first complete remission.[8] The selection process was further refined by measurement of minimal residual disease.[9]

Meanwhile, the routine use of FLT3 inhibitors, such as midostaurin and quizartinib, and IDH inhibitors in patients with the respective mutations, gemtuzumab-ozogamicin in CD33-positive cases, and the use of CPX-315 for those with adverse genetic alterations, has led to further improvements in induction therapy. And it can be expected that still more improvements will be seen with menin inhibitors for *NPM1*-mutated and *KMT2A*-rearranged patients.

While the data from the HARMONY Alliance also show improvements of intensive induction therapy in patients >60 years, roughly 70% of the patients were <60 years (Table 1). In these patients and especially in those >65 years treatment with hypomethylating agents plus venetoclax has nowadays replaced ”3+7“ induction chemotherapy and the data in the report by Sobas *et al*. will be difficult to compare because of the larger differences in selection criteria.[3] This will also hold true for the more widely used allo-HCT consolidation in the elderly since substantially more elderly patients obtain a complete remission, and also allo-HCT has improved over the last 20 years.[10]

Despite all these limitations, the HARMONY Alliance can be congratulated for this large pan-European dataset of real-world patients which will provide a useful comparator to evaluate the results of targeted therapies including minimal residual disease assessment for consolidation therapies in the future.

Disclosures

No conflicts of interest to disclose.

References

1. Sobas M, Turki AT, Villaverde A, et al. Outcomes with intensive treatment for acute myeloid leukemia over two decades. An analysis of the HARMONY Alliance. Haematologica. 2025;110(5):1126-1140.
2. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447.
3. DiNardo CD, Erba HP, Freeman SD, Wei AH. Acute myeloid leukaemia. Lancet. 2023;401(10393):2073-2086.
4. Juliusson G, Hagberg O, Lazarevic VL, et al. Improved survival of men 50 to 75 years old with acute myeloid leukemia over a 20-year period. Blood. 2019;134(18):1558-1561.
5. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. N Engl J Med. 1994;331(14):896-903.
6. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356(4):348-359.
7. Azoulay E, Maertens J, Lemiale V. How I manage acute respiratory failure in patients with hematological malignancies. Blood. 2024;143(11):971-982.
8. Schlenk RF, Döhner K, Krauter J, et al.; German-Austrian Acute Myeloid Leukemia Study Group. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med. 2008;358(18):1909-1918.
9. Heuser M, Freeman SD, Ossenkoppele GJ, et al. 2021 update on MRD in acute myeloid leukemia: a consensus document from the European LeukemiaNet MRD Working Party. Blood. 2021;138(26):2753-2767.
10. Bazarbachi A, Labopin M, Moukalled N, et al. Improvements in posttransplant outcomes over two decades in older patients with acute myeloid leukemia in the EBMT ALWP study. Clin Cancer Res. 2024;30(9):1778-1787.