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

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In the present issue of Haematologica, Sobas et al present the findings of the pan-European AML dataset of the HARMONY Alliance on the improvements of treatment outcome in a large cohort (n=5359) of adult patients (age, 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 hemopoietic cell transplantation (allo-HCT) over two decades from 1997-2016 (1). Patients with acute promyelocytgic leukemia, mixed-lineage AML, and AML of ambiguous lineage were excluded. The distribution of the ELN2017 risk categories was comparable in the four cohorts (Table 1) (2). None of the patients received targetted therapy. The median overall survival time (OS) significantly increased from 15.5. months to 37.8 months. While the complete remission rate remained unchanged over the different time periods, the 30-day and the 60-day mortality significantly improved (Table 1). In ELN favourable- and intermediate-risk groups, overall survival only improved over time in the non-transplanted patients, while in the high-risik group both non-transplanted and transplanted patients showed improved survival.

Why are these data interesting in a time where targeted drugs like FLT3- and – to a lesser degree - IDH1/2 inhibitors have become standard additions to the „3+7" induction protocols and where elderly and unfit patients are regularly treated with hypomethlyating agents and venetoclax (3)? Although previous publications have demonstrated improvement in treatment outcome over time (4), the present data covered patients treated in prospective clinical trials and real-world setting outside trials in >100 leukemia treatment centers thereby being representative. Since the induction therapy was similar in the centers, the decrease in early mortality from 13% in the first to 4.7% in the last treatment period, indicates a better supportive care with better experience with high-dose ara-C after the publication by Mayer et al in 1994 (5), broader use of antiinfective agents including antifungals (6), easier access to intensive care units (7), and probably the 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-risik group (2). While it is conceivable that in ELN-2017 low-risk patients allo-HCT in first CR did not improve overall survival, the results in the intermediate-risk group which show some fluctuation in the fraction of patients going on to alloHCT, might reflect the change in patient selection occuring after publication of the seminal paper by Schlenk et al in 2000 which indicated that *FLT3*-mutated AML patients should be transplanted in CR1 (8). This selection processes were further refined by the measurement of MRD (9).

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

While the data of the HARMONY Alliance also show improvements of intensive induction therapy in patients >60 years, roughly 70% of the patients are <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 this publication will be difficult to compare because of the larger differences in selection criteria (3). This will also hold true for the more widely used alloHCT consolidation in the elderly since substantially more elderly patients obtain a CR, and also allo-HCT has improved over the last 20 vears (19)

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

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Table 1: Characteristics of the AML cohorts according to time periods of diagnosis

Characteristics	1997-2002 (n=1127)	2002-2006 (n=1294)	2007-2011 (n=1821)	2012-2016 (n=1117)
Age (median) Range	55 (17-84)	51 (15-85)	53 (16-86)	55 (17-85)
Female sex (%)	45.2	47.9	46.8	46.2
ELN 2017 (%)				
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

Abbreviations: ELN, European LeukemiaNet