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Is age just a number? Intensive therapy for core binding factor acute myeloid leukemia in older adults

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In this issue of *Haematologica*, Mosna et al.[1] assess the outcomes of older patients with core binding factor acute myeloid leukemia (CBF-AML) managed with intensive chemotherapy and provide important insights into this understudied subgroup (**Figure**).

CBF-AML refers to AML with one of two cytogenetic abnormalities – t(8;21) and inv(16)/t(16;16) – which alter how subunits of the "core binding factor" complex bind target genes. The aberrant transcription that ensues arrests hematopoietic differentiation, resulting in leukemia. CBF-AML typically occurs *de novo* in younger patients where it makes up ~10-15% of cases.[2] However, CBF-AML comprises ~5% of AML cases diagnosed in individuals over 60 years.[3]

CBF-AML is uniquely chemo-sensitive as an anthracycline and cytarabine-based induction almost always induces a complete remission (CR), and repetitive courses of high-dose cytarabine frequently cure patients, but most of the data is in younger cohorts.[2,4-7] In the current era, where hypomethylating agent (HMA)-based regimens are replacing anthracycline and cytarabine-based chemotherapy in older patients with AML, renewed attention to the performance of the traditional approach in older patients with CBF-AML is needed.

Mosna et al. retrospectively analyzed 229 patients with CBF-AML ≥60 years (median 66.2 years, 26% ≥70 years) across 37 institutions in the United States and Europe.[1] Most (88%) of the cohort received an anthracycline during induction, with patients ≥70 years slightly less likely to receive an anthracycline than younger patients (78% vs 91%, p=0.02).

The CR rate for this older cohort was an impressive 84%! Additionally, there was no statistical difference in CR attainment by age (86% vs 78%, for younger [<70 years] and older [≥70 years] patients, respectively), but receipt of an anthracycline significantly improved the chance of reaching CR (86% vs 68%, p=0.03). For comparison, consider CALGB 8461 where 1213 patients with de novo AML (15-86 years; 36% >60 years) were induced with an anthracycline plus cytarabine and 88% of patients with CBF-AML achieved CR.[5] Similarly, in SWOG 0106, where patients ≤60 years received induction with daunorubicin and cytarabine +/- gemtuzumab ozogamicin, the CR rate for patients with CBF-AML in the control arm was very high (93%).[8] The French AML Intergroup focused on patients ≥60 years with CBF-AML induced with an anthracycline plus cytarabine on multiple French trials and showed a CR rate of 80%, just slightly lower than the rate in studies of younger patients.[9] Mosna et al. now confirm in a larger, international cohort that CBF-AML in older patients, including patients ≥70 years, is chemo-sensitive and almost as likely to respond to an anthracycline and cytarabine induction as CBF-AML in younger patients, specifically when an anthracycline is delivered.[1]

Although older patients with CBF-AML achieve CR with similar frequency to younger patients, Mosna et al. confirm that overall survival (OS) is inferior.[1] The French AML Intergroup study of older CBF-AML patients reported a 5-year OS of 31%.[9] In comparison, the German AML Intergroup reported a 5-year OS of 65%-74% among younger patients aged 16-60 with CBF-AML.[10] With a median follow-up of 53.5 months, Mosna et al. reported a 5-year OS of 44%; patients ≥70 years had inferior 5-year OS (33%) compared to patients <70 years (48%, p=0.006). Most deaths were from leukemia although non-relapse mortality was non-trivial (~25%, without major differences by age cohort). The main factor affecting OS was achievement of CR, which was in turn influenced by receipt of an anthracycline. Among those achieving CR, most (88%) received some cytarabine consolidation with younger patients more likely to receive ≥3 courses (32% vs 20%, p=0.086). Transplant in this cohort was rare. The authors studied the impact of overall treatment dose intensity on event-free survival (EFS) and found that outcomes were improved in those receiving more chemotherapy (5-year EFS of 49% vs 25% vs 17%, if ≥3 vs 1-2 vs no courses of cytarabine), an association confirmed in a multivariate analysis. It must be recognized, however, that determining causation versus correlation is not possible in a retrospective study.

In this issue of *Haematologica*, Mosna et al. conveys to the leukemia clinician that an anthracycline plus cytarabine induction will usually induce a CR in an older patient with CBF-AML, and receipt of ≥3 courses of cytarabine consolidation is associated with better EFS and OS (even in the absence of transplant), confirming findings in younger cohorts.[1,6,7] What is not answered, however, is whether older patients received less chemotherapy due to toxicity or refusal, or whether clinicians have been remiss in offering optimally effective therapy due to fear of harm. Additionally, the study does not establish the minimum dose of cytarabine in consolidation needed to achieve benefit.

Although encouraging that more fit older patients may benefit from conventional approaches, it is also clear that many older patients will not be eligible to (or may not

desire to) receive anthracycline and/or high doses of cytarabine due to cardiac, neurologic, and other comorbidities and thus alternative approaches are needed. Older patients with CBF-AML were excluded from the pivotal trials of HMA and venetoclax, but Zhang et al. published a retrospective, single center study of azacitadine and venetoclax in patients with newly diagnosed CBF-AML unfit for intensive chemotherapy and reported responses in 4/13 (31%) of patients with t(8;21) and 17/17 (100%) of patients with inversion (16), suggesting a possible therapeutic alternative.[11]

In summary, Mosna et al. enhance our understanding of CBF-AML in older adults and charges the leukemia community to conduct more research to define the role of conventional (anthracycline plus cytarabine) and newer (hypomethylating agent and venetoclax) chemotherapy approaches, as well as the role of allogeneic transplantation, in this population ideally including additional variables such as co-mutations and measurable residual disease (MRD).

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Legend: Core binding factor acute myeloid leukemia in older adults: Incidence, approach, and outcomes in patients ≥ 60 years old treated with intensive chemotherapy as reported by Mosna et al.

Core binding factor Acute myeloid leukemia

- ~5% of AML cases in those ≥ 60 years old
- Anthracycline and cytarabine sensitive

Optimal treatment for patients with CBF-AML ≥ 60 years old

> 75 years old ?
Frail
Cardiac history

Younger
Robust
Normal organ function

Outcomes in patients ≥ 60 years old with CBF-AML treated with intensive chemotherapy

Median age	CR (%) by induction regimen		5-year EFS (%) by cytarabine dose intensity		
	Anthracycline used	No anthracycline	No consolidation	1-2 cycles	≥ 3 cycles
67	86	68	18	26	49