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 1).

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 in whom it accounts for ~10-15% of cases.[2] However, CBF-AML comprises ~5% of AML cases diagnosed in individuals over 60 years old.[3]

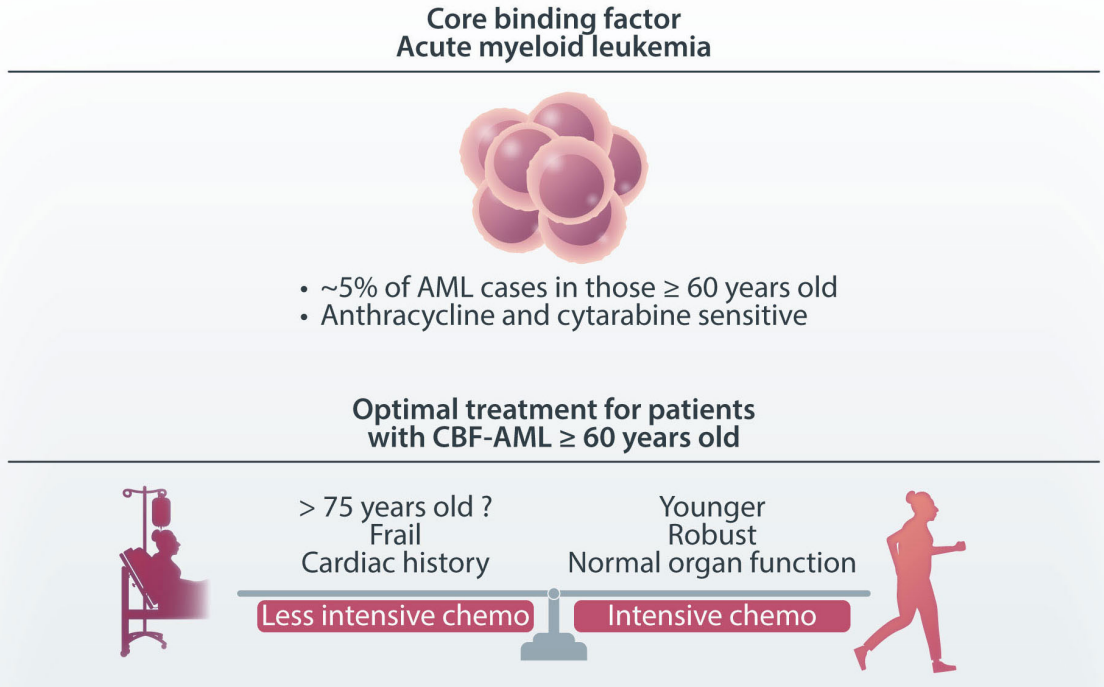
CBF-AML is uniquely chemosensitive as an anthracycline and cytarabine-based induction almost always induces a complete remission (CR), and repetitive courses of high-dose cytarabine frequently cure patients, although most of the data come from younger cohorts.[2,4-7] In the current era, in which hypomethylating agent-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 who were ≥60 years old (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 old slightly less likely to receive an anthracycline than younger patients (78% *vs*. 91%, *P*=0.02).

The CR rate in 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 the CALGB 8461 study in which 1,213 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 the SWOG 0106 study, in which 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 old, is chemosensitive and almost as likely to respond to 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 that in younger patients, Mosna *et al*. confirm that overall survival is inferior.[1] The French AML Intergroup study of older CBF-AML patients reported a 5-year overall survival of 31%.[9] In comparison, the German AML Intergroup reported a 5-year overall survival of 65%-74% among younger patients (aged 16-60 years) with CBF-AML.[10] With a median follow-up of 53.5 months, Mosna *et al.* report a 5-year overall survival of 44%; patients ≥70 years had inferior 5-year overall survival (33%) compared to patients <70 years (48%, *P*=0.006). Most deaths were from leukemia although non-relapse mortality was not trivial (~25%, without major differences by age cohort). The main factor affecting overall survival 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). Transplantation in this cohort was rare.

The authors studied the impact of overall treatment dose intensity on event-free survival and found that outcomes were improved in those receiving more chemotherapy (5-year event-free survival 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



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

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

Figure 1. 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.*[1] AML: acute myeloid leukemia; CBF-AML: core-binding factor acute myeloid leukemia; CR: complete remission; EFS: event-free survival.

determining causation *versus* correlation is not possible in a retrospective study.

In this issue of *Haematologica*, Mosna *et al*. convey 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 event-free and overall survival (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 not offering optimally effective therapy due to fear of harming the patient. Additionally, the study does not establish the minimum dose of cytarabine in consolidation needed to achieve benefit.

Although it is encouraging that more fit, older patients may benefit from conventional approaches, it is also clear that many older patients will not be eligible for (or may not desire) treatment with an anthracycline and/or high doses of cytarabine due to cardiac, neurological, and other comorbidities and thus alternative approaches are needed. Older patients with CBF-AML were excluded from the pivotal trials of hypomethylating agents 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 charge the leukemia community to conduct more research to define the role of conventional chemotherapy approaches (anthracycline plus cytarabine) and newer ones (hypomethylating agent and venetoclax), as well as the role of allogeneic transplantation, in this population ideally including additional variables such as co-mutations and measurable residual disease.

Disclosures

MRL has received research funding (to her institution) from AbbVie and Novartis; and has sat on ad hoc advisory boards for Novartis, Pfizer, KITE, and Jazz. BMG holds equity as a co-founder of Btwo3 Therapeutics and Inograft Biotherapeutics.

Contributions

BMG and MRL wrote the manuscript.

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