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MYELOID NEOPLASIA

Comment on Itzykson et al, page 507

A slow-go prognosis for older patients with newly diagnosed AML

Gary Schiller | UCLA Health Sciences

To determine which older patients may derive benefit from the prolonged pancytopenia and hospitalization associated with cytarabine-based induction chemotherapy, Itzykson et al, in this issue of *Blood*, report on a convenient clinical prognostic tool. The instrument, based on cytogenetic and molecular profiling, identifies which group of older and fit patients with newly diagnosed acute myeloid leukemia (AML) may derive survival benefit from intensive induction and consolidation chemotherapy.[1]

The clinical and biologic features of AML in older adults denote aggressive disease biology and poor likelihood of long-term survival, regardless of remission-induction and consolidation strategies.[2] Unfortunately, at least half of all patients with AML are within the demographic of those age >60 years at diagnosis.[3] Many of these patients, in developed countries, are sufficiently fit to be offered intensive cytotoxic induction therapy and allogeneic transplantation, treatment that, for years, has offered an opportunity for long-term survival free of AML in younger patients. Feasibility, however, does not define success.[4] In these otherwise vigorous older patients, adverse molecular and/or cytogenetic features of leukemia are common, and patients often present with a history of antecedent hematologic disorder (typically longstanding anemia, myelodysplasia, or myeloproliferative neoplasm) or prior cytotoxic chemotherapy or radiotherapy, conferring poor prognosis. Despite inherent selection at specialty centers, life-threatening toxicities of therapy still occur in older patients who have no prior comorbid conditions. Even if the incidence of infection or organ toxicity can be mitigated, older patients are still less likely to achieve complete remission

AML prognostic scoring systems

Prognostic scoring system	Subgroup	Defining features
ELN 2010[9]	Favorable	t(8;21); RUNX1-RUNX1T1; inv(16);CBFB-MYH11; mNPM1, no flt3 ITD; mCEBPA; mNPM1 + flt3 ITD*; wtNPM1 + flt3 ITD*
	Intermediate-1	wtNPM, no flt3 ITD*; t(9;11); MLL
	Intermediate-2	t(6;9); inv(3); other cytogenetics
	Adverse	−5, del (5q); −7; abnl17p; complex
ELN 2017[5]	Favorable	Similar to above; mNPM1 + flt3 ITD-low; biallelic mCEBPA
	Intermediate	mNPM1 and flt3-ITD (high); t(9;11); other cytogenetics
	Adverse	t(6;9); t(9;22) inv3; −5, del(5q); −7; abnl17; mRUNX1; mASXL1; mTP53; flt3 ITD-high
ALFA 2021[1]	Favorable (go-go)	Non–poor-risk cytogenetics + mNPM1 with ≤1 of the following: flt3 ITD-low, mDNMT3a, mASXL1, mNRAS
	Intermediate (slow-go)	All others
	Unfavorable (no-go)	Adverse cytogenetics ≥1 of the following: mKRAS, mTP53

ELN, European LeukemiaNet; ITD, internal tandem duplication; m, mutated.
*Normal karyotype.

and sustained survival. Because of high-risk disease features, many treating physicians opt for less-intensive induction therapy, today defined as a regimen including either glasdegib plus cytarabine or the BCL2 inhibitor venetoclax plus a hypomethylating agent. For both physician and patient, such a regimen involves logistic challenges in providing support through a period of prolonged and recurrent cytopenia, as does treatment with cytarabine and anthracycline. Weighing the impact of clinical history, comorbid conditions, and biologic risk when determining which therapy to administer is challenging and inconsistently applied.

In their report, Itzykson and colleagues from several treatment centers in France describe a simple prognostic instrument, based on results of cytogenetic and molecular sequencing, used in their Acute Leukemia French Association (ALFA) 1200 study to identify which fit older patients may derive benefit from intensive induction chemotherapy with cytarabine and anthracycline for newly diagnosed AML. On the basis of statistical modeling of karyotypic abnormalities and a panel of molecular diagnostics, they identified 7 genes commonly mutated in AML of prognostic value. Using a simple point-based tool, the authors identified 3 distinct groups of patients receiving intensive therapy whose survival outcome at 2 years could be predicted. In applying the tool to AML patients in a validation group, the authors defined 1 group as go-go (favorable outcome predicted), another as no-go (extremely unfavorable outcome predicted), and a third as slow-go (unfavorable outcome predicted, but with an estimated probability of survival of 39%) with regard to the use of intensive induction.

A major advantage of the tool from the ALFA group, over others such as that defining risk groups from European LeukemiaNet,[5] is that it is simple and does not consider the many distinct combinations of single-gene mutations that result from commercial panels (see table). A challenge is that molecular markers would be expected a priori to typically predict poor response in a group of older patients with AML, in whom disease is typically limited to either intermediate or adverse cytogenetic risk. Discriminating within this group on the basis of molecular predictors might have been possible in the current study, in which very few patients underwent allogeneic transplantation and in which salvage options for patients after relapse would have been limited as well. Outside of those limitations, the predictive value of the tool will need further evaluation. In the ALFA study, the decision tool was further restricted to those patients treated with myelosuppressive cytarabine-based induction and consolidation regimens. How the tool would operate if patients were treated with alternative agents, such as the liposomal combination drug of daunorubicin and cytarabine, or with venetoclax and a hypomethylating agent is not yet known.

Therapy for AML in older patients involves not only cytarabine-based induction and consolidation and glasdegib- or venetoclax-based regimens, but also combination therapy including drugs that target distinct gene mutations,[6] pharmacokinetically modified cytotoxic therapy,[7] and immunotherapy in the form of gemtuzumab[8] or allogeneic transplantation. We do not know how a model derived from cytarabine-based therapy alone would perform with variation in treatment.

Several conclusions may be drawn from the report by Itzykson et al. First, and most obvious, is the impact in the last several years of molecular diagnostics in hematologic neoplasia. One problem for our patients has been that leukemia must be defined today by its predominant cytogenetic and molecular profiles rather than by its diagnostic code. Second, the impact of statistical instruments that define prognosis based on outcome after intensive therapy is limited by the large percentage of older fit patients (53% in this study) whose disease characteristics place them in an intermediate group (the slow-go group). Third, for this slow-go group, which comprises a majority of older patients with AML, we await results of a prospective trial of intensive cytarabine-based therapy vs nonintensive but myelosuppressive venetoclax-based therapy. Such a study must include randomization with stratification for cytogenetic and molecular risks in order to report outcomes including remission induction, nonrelapse mortality, and survival, as well as use of supportive care resources, incidence and feasibility of allogeneic transplantation, and quality of life. Continuing to treat the slow-go group with business-as-usual cytotoxic induction treatment is really a no-go.

Conflict-of-interest disclosure: G.S. has received research support from AbbVie, Agios, Astellas, Pfizer, and Jazz Pharmaceuticals. ■

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DOI 10.1182/blood.2021012456