Prognostic Significance of Molecular Markers and Targeted Regimens in the Management of Acute Myeloid Leukemia

Presented by Martin Tallman, MD

Abstract

The diagnosis, staging, and treatment of acute myeloid leukemia (AML) has evolved based on identification of important genetic alterations and drugs to target those genes. Cytogenetic abnormalities play a major role in managing AML. Achieving minimal residual disease is an increasingly important milestone. Four new targeted therapies are now available for the treatment of AML.

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In 2018, state-of-the-art treatment for acute myeloid leukemia (AML) is characterized by 6 features:

- Defined by cytogenetic and molecular interactions,
- Intensified induction/less intensive consolidation,
- Increased importance of minimal residual disease (MRD),
- Expanded availability of allogeneic transplantation,
- Paradigm shift in older patients, and
- Incorporation of novel agents.

With increased understanding of the biological underpinnings of AML, it is possible to characterize patients according to molecularly defined risk groups. Patients with adverse risk comprise 34% of all patients, those with intermediate-risk disease account for 21%, and those with favorable risk account for 45%.¹

“Over the last decade, there has been a dramatic increase in the knowledge of molecular genetics,” Martin Tallman, MD, Chief, Leukemia Service, Memorial Sloan Kettering Cancer Center, and Professor of Medicine, Weill Cornell Medical College, told listeners at

the NCCN 23rd Annual Conference (Figure 1).² “It is becoming increasingly important to become aware not only of a particular mutation but of the spectrum of mutations that occurs in a given patient. They have important interactions that lead to dramatic differences in overall survival (OS),” he explained. Dr. Tallman is also Vice Chair of the NCCN Guidelines Panel for AML.

For example, patients who are CEBPA-positive have the best survival if they are *FLT3* wild-type (*FLT3*^{wt}) and *NPM1*^{mutant}. Survival is worst with *FLT3*^{ITD} and *NPM1*^{wt}. Intermediate survival is observed for *FLT3*^{ITD}/*NPM1*^{mutant} and *FLT3*^{wt}/*NPM1*^{wt}.³ Further complicating the picture is that a patient can be *FLT3*^{ITD}-positive and fall into favorable, intermediate, and adverse risk categories, according to the 2017 European LeukemiaNet (ELN) risk stratification (Figure 2).² Essentially, an additional factor that influences risk is the allelic burden, or as illustrated in this context, how positive a patient is for the *FLT3*^{ITD} mutation.

In general, older adults with AML tend to have a less favorable prognosis. Patients with favorable-risk AML (*NPM1* mutations and mutations in other genes) can experience an overall complete remission rate of 81%, disease-free survival rates of 46%, and OS rate of 45%. In contrast, older patients with poor-risk AML (without *NPM1* mutations) have a complete remission rate of 32%, disease-free survival rate of 2%, and OS rate of 4%.⁴

Next-generation sequencing and flow cytometry before transplantation are important assessment tools

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Figure 1. Molecular classes of acute myeloid leukemia (AML) and recurrent gene mutations shows the complexity of the genetics of AML. Reprinted with permission from the American Society of Hematology © 2017. 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;129:424-447.

that can be used to predict outcomes after transplantation. If no evidence of MRD is found using flow cytometry and next-generation sequencing before transplantation, the outcome is likely more favorable than if either test is MRD-positive.

"Many institutions are turning to multiplex testing in AML," Dr. Tallman noted. "However, some of these gene mutations are important in everyday practice and are 'clinically actionable.' Every patient with newly diagnosed AML should be tested for these genes," Dr. Tallman said.

Newly Approved and Emerging Drugs

For the first time in 45 years, new drugs have been FDA-approved or were given breakthrough designation for AML: midostaurin (FLT3 inhibitor) for patients with FLT3 mutations and are treatment-naïve; gemtuzumab ozogamicin (GO; anti-CD33) for patients who are CD33-positive with core binding factor and possibly intermediate risk who are treatment-naïve (and may also be used in patients with relapsed/refractory AML); enasidenib (IDH2 inhibitor) for relapsed/refractory AML with IDH2 mutations; CPX-351 (new 5:1 liposomal formulation of cytarabine and daunorubicin) for treatment-naïve

patients with therapy-related AML (t-AML) or AML with myelodysplasia-related changes (MRC); and venetoclax (BCL-2 inhibitor) for treatment-naïve patients with low-dose cytarabine.

Midostaurin

Midostaurin was approved by the FDA for induction and consolidation based on the RATIFY trial, which took 13 years to complete.⁵ The study showed that patients with FLT3 mutations (ITD or WT) had a 4-year survival of 51.4% on midostaurin ver-

Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1
	inv(16)(p13.1q22) or t(16;16)(p13.1q22); CBFB-MYH11
	Mutated NPM1 without FLT3-ITD or with FLT3-ITD ^{low}
Intermediate	Biallelic mutated CEBPA
	Mutated NPM1 and FLT3-ITD ^{high}
	WT NPM1 without FLT3-ITD or with FLT3-ITD ^{low} without advanced genetics
Adverse	t(9;11)(p21.3;q23.3); MLLT3-KMT2A
	Cytogenetic abn not classified as favorable or adverse
	t(6;9)(p23;q34.1); DEK-NUP214
	t(v;11q23.3); KMT2A rearranged
	t(9;22)(q34.1); BCR-ABL1
	inv(3)(q21.3q26.2) or t(3;3)(q21.3q26.2); GATA2-MECOM(EV11)
	-5 or del(5q); -7; -17/abn(17p)
	Complex karyotype, monosomal karyotype
	WT NPM1 and FLT3-ITD ^{high}
	Mutated RUNX1, ASXL1, or TP53

Figure 2. 2017 ELN risk stratification by genetics.

Abbreviation: WT, wild-type

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sus 44.2% on placebo ($P=.0074$), and the benefit was most pronounced in *NPM1*^{wt} and *FLT3*^{high} patients.

“This study is practice-changing, but more information is required to determine clinically meaningful impact based on long-term studies. The OS benefit is only 7%,” Dr. Tallman said, “and the benefit was greater in patients with the *FLT3*^{TKD} mutation when compared with those with the *FLT3*^{ITD} mutation, who have less favorable risk. Additionally, midostaurin is approved in Europe for maintenance, but not in the United States. We are not clear which phase of the disease is most important.”

Midostaurin is among the least potent *FLT3* inhibitors. More potent *FLT3* inhibitors in development are gilteritinib, quizartinib, and crenolanib.

Gemtuzumab Ozogamicin

GO was approved by the FDA in 2000, withdrawn, and then reintroduced. Currently, it is given in a fractionated schedule to reduce toxicity. An OS benefit is seen in favorable-risk patients and a trend toward improved survival is seen in intermediate-risk patients. Event-free survival was significantly improved with GO plus daunorubicin and cytarabine versus daunorubicin and cytarabine in the ALFA-0701 trial of patients aged 50 to 70 years with newly diagnosed AML ($P=.003$).⁶

CPX-351

CPX-351 uses a nanoscale delivery complex and is a fixed molar ratio of cytarabine to daunorubicin (5:1) to increase cytotoxicity.⁷ A randomized phase III trial found that CPX-351 improved response rates and OS compared with the conventional “7+3” regimen (cytarabine 7 days and daunorubicin 3 days). Complete response was seen in 37.3% of patients on CPX-351 versus 25.6% with the 7+3 regimen; median OS in the CPX-351 versus placebo groups were 9.56 versus 5.95 months, respectively ($P=.005$). A preliminary subset analysis suggested that, compared with patients treated with the 7+3 regimen, those treated with CPX-351 who went on to allogeneic transplant had considerably improved median survival (10.25 months vs not reached, respectively).⁸

Enasidenib and Ivosidenib

IDH is a cancer-associated metabolite that blocks normal cellular differentiation. A phase II study of the IDH2 inhibitor enasidenib in patients with relapsed/refractory AML showed an overall response rate of 37%, complete morphologic remission in

20% of patients, and stable disease in approximately 40% to 50%.^{9,10}

Molecular complete response is seen in approximately 34% of patients with relapsed or refractory AML and 60% of previously untreated patients treated with the IDH inhibitor ivosidenib.⁹ Adverse events include differentiation syndrome, which can occur late (median, 48 days; range, 10–340 days).¹⁰ Complete response was seen in 21% by cycle 3, 68% by cycle 5, and 82% by cycle 7.¹⁰ The longest duration of complete response observed was >30 months. RAS mutations were associated with nonresponse to IDH inhibition.¹¹ “It can take up to 7 months to achieve complete response, and therefore it requires patience to use these drugs,” Dr. Tallman said.

Next-generation trials are being planned or in progress with IDH inhibitors, including induction chemotherapy with and without IDH inhibitors, hypomethylating agents with or without IDH inhibitors, and IDH inhibitors combined with *FLT3* inhibitors, venetoclax, or CPX-351.

Venetoclax

Venetoclax is a BCL2 inhibitor that sequesters proapoptotic proteins and initiates apoptosis. Venetoclax received a breakthrough therapy designation from the FDA for use in combination with low-dose cytarabine based on 2 major studies.^{12,13}

“Response rates to venetoclax and cytarabine or azacitidine are impressive in previously untreated older adults with AML, who typically have a less favorable response,” Dr. Tallman stated. “In the studies with venetoclax and low-dose cytarabine, you can say that in AML, the rich get richer. Those who fare well are destined to fare well because of genetics. Outcomes are less favorable when *p53* mutations are present. In addition, you see rapid [within 1 month] peripheral blood clearance and clearance of leukemia stem cells with venetoclax and azacitidine treatment.”

Expanded Options for Induction Chemotherapy in Younger Patients

Typically, intensive induction chemotherapy with the 7+3 regimen is used. Since 2017, in patients with *FLT3* mutations (either ITD or tyrosine kinase domain [TKD]), midostaurin may also be given after induction on days 8 to 21 and during consolidation chemotherapy. CPX-351 can be given for second-

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ary AML or AML with MRC. GO can be given to patients who are CD33-positive with 7+3 induction and consolidation therapy on days 1, 4, and 7 or as a single agent days 1 and 8.

The 2018 NCCN Guidelines for AML state that after standard-dose cytarabine induction, bone marrow biopsy should be performed 14 to 21 days later. Patients who experience complete response go on to consolida-

tion postremission therapy (depending on risk factor status). For induction failure, matched transplant or high-dose cytarabine (alone or with another induction regimen) are recommended options. A clinical trial is recommended for all patients, including those with relapsed/refractory disease, Dr. Tallman continued. For patients who are candidates for intensive chemotherapy, treatment is guided by genetics.

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