Acute Myeloid Leukemia: An Ever-Changing Disease

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Abstract

Acute myeloid leukemia is the most common form of acute leukemia in adults. In recent years, there has been robust characterization of molecular targets for drug development, leading to the U.S. Food & Drug Administration approval of numerous new treatments during 2017 and 2018. In light of these new approvals, this article provides an update for advanced practitioners on risk stratification, which is critical for guiding treatment selection.

Acute myeloid leukemia (AML) is a malignant disease that results from the abnormal proliferation and differentiation of myeloid stem cells in the bone marrow (De Kouchkovsky & Abdul-Hay, 2016). Cells are arrested in development within the myeloid lineage, which leads to an abnormal accumulation of blasts or immature cells. According to the World Health Organization (WHO) criteria, AML is characterized by 20% or more of blasts in the bone marrow or peripheral blood (Vardiman, Harris, & Brunning, 2002). It is the most common form of acute leukemia seen in adults, with an estimated 21,450 new AML cases diagnosed in 2019 (Siegel, Miller, & Jemal, 2019). It has a slightly higher prevalence among males over females, with a median age at diagnosis of approximately 68. Unfortunately, the estimated number of deaths attributed to AML in 2019 is nearly 11,000, which is approximately 1.8% of all cancer deaths in the United States (National Institutes of Health, 2019).

PATHOPHYSIOLOGY

Mutations that lead to the abnormal maturation of healthy bone marrow cells or proliferative growth of immature cells results in AML. Research from the Cancer Genome Atlas Research Network has demonstrated that AML arises from a founding clone and at least one subclone, and mutations in epigenetic regulation, such as in *IDH1* or *IDH2*, occur early in AML evolution (Döhner, Weisdorf, & Bloomfield, 2015). Multiple different mutations that are thought to play a role in the development of AML have been identified and include those that affect tumor suppressor genes, chromatin modification, RNA processing, and

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chromosome segregation. For example, mutations in signaling proteins such as FLT3 promote proliferation through the RAS/JAK/AKT signaling pathway and IDH mutations affect DNA methylation (Döhner, Weisdorf, & Bloomfield, 2015; The Cancer Genome Atlas Research Network, 2013).

RISK FACTORS

There are several potential causative factors that contribute to the underlying etiology of AML. Some cases of AML have known risk factors, whereas approximately 74% of patients develop de novo AML without any identifiable risk (Hulegardh et al., 2014). Known risk factors for AML include prior chemotherapy, antecedent hematologic disorders, chemical exposures, congenital disorders, and environmental exposures (Stock & Thirman, 2019). Antecedent hematologic disease–associated AML (considered a secondary AML) occurs in approximately 19% of cases (Hulegardh et al., 2014). The most common identifiable risk would be antecedent hematologic disorders like myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), or aplastic anemia (Stock & Thirman, 2019).

Patients who received prior chemotherapy are at higher risk of developing AML, which is referred to as therapy-related AML (a type of secondary AML), and is particularly associated with alkylating agents, topoisomerase II inhibitors, ionizing radiation, and certain antimetabolites and antitubulin agents (Bueso-Ramos, Kanagal-Shamanna, Routbort & Hanson, 2015; National Comprehensive Cancer Network [NCCN], 2019; Shuryak et al., 2006). Therapy-related AML accounts for approximately 8% of AML cases and develops a median of 4 to 7 years following alkylating agents or radiation therapy, 2 to 3 years after topoisomerase II inhibitor exposure, or 1 to 2 years following hematopoietic cell transplant for the primary malignancy (Bhatia, 2013; Hulegardh et al., 2014). High levels of exposure to benzenes have an association with developing leukemia and *RAS* mutations, suggesting induced genetic damage culminating in acute leukemia (Bhatia, 2013). Genetic abnormalities that increase the risk of developing AML include, but are not limited to, Fanconi anemia, Li-Fraumeni syndrome, and Down syndrome. Mutations like *RUNX1* have been associated with familial platelet disorder with the risk of development of AML, whereas mutations in *CEBPA* have been seen in families with AML in an autosomal dominant pattern (Goldin et al., 2012).

RISK STRATIFICATION

Cytogenetics and genetic mutations also serve as prognostic markers that are used for stratifying disease by risk (NCCN, 2019). This risk stratification is critical for treatment decisions. Previously, evaluation for genetic mutations was done by targeted assays. However, next-generation sequencing (NGS) has resulted in new insights about variations in DNA. More specifically in AML, understanding of the disease, prognosis, and treatment has changed from this new knowledge.

The most common mutations found in AML include *FLT3* (37%), *NPM1* (29%), *DNMT3A* (23%), and *NRAS* (10%; Table 1; Patel et al., 2012). Mutations can occur concurrently; for example, *IDH1* or *IDH2* mutations may be present with *NPM1* mutations, and *FLT3*-ITD mutations may be present with either *CEBPA*, *TET2*, *DNMT3A*, or *MLL*–partial tandem duplication alterations. These and other mutations that are less common have been found to confer prognostic information, such as reduced overall survival (OS) with *FLT3*-ITD mutations or improved OS with *IDH2* mutations. Therefore, the information that is learned from NGS can help guide treatment selection, provide prognostic information, and help practitioners educate their patients.

Next-generation sequencing, or other molecular testing, is recommended as part of the NCCN Guidelines for AML (NCCN, 2019). The NCCN Guidelines do not specify that molecular testing be done by NGS, but because of the availability of new targeted agents, NGS (to include *IDH1* and *IDH2*, among others) should be performed. The NCCN Guidelines recommend the following tests as part of the workup for AML (NCCN, 2019):

- Complete blood count with manual differential and routine chemistry profile (including liver function tests and levels of serum creatinine, lactate dehydrogenase, and uric acid)
- Coagulation profile
- Bone marrow aspiration and biopsy, including classical cytogenetics, immunophenotyp-

Table 1. Common Mutations (≥ 5%) Found in Acute Myeloid Leukemia

Gene	Overall frequency (%)	Prognosis
FLT3 (ITD and TKD)	37	Reduced OS (*FLT3*-ITD)
NPM1	29	Reduced OS if no concurrent mutations in *IDH1/2*
DNMT3A	23	Reduced OS in intermediate-risk AML; poor prognosis with concurrent *FLT3*-ITD
NRAS	10	Intermediate prognosis
CEBPA	9	Improved OS; intermediate prognosis if concurrent with *FLT3*-ITD
TET2	8	Reduced OS in intermediate-risk AML; poor prognosis with concurrent *FLT3*-ITD
WT1	8	Intermediate prognosis
IDH2	8	Improved OS (particularly *R140Q* mutation)
IDH1	7	Intermediate prognosis
KIT	6	Reduced OS (t[8;21] core-binding–factor mutation)
RUNX1	5	Intermediate prognosis
MLL-PTD	5	Reduced OS; poor prognosis with concurrent *FLT3*-ITD

Note. AML = acute myeloid leukemia; ITD = internal tandem duplication; OS = overall survival; PTD = partial tandem duplication; TKD = tyrosine kinase domain. Information from Patel et al. (2012).

ing, and molecular testing for *c-KIT*, *FLT3*-ITD, *NPM1*, *CEBPA*, and other mutations
- Human leukocyte antigen typing of patient and family.

Once cytogenetics and molecular testing is completed, risk stratification should be performed, which will ultimately guide treatment decisions (NCCN, 2019). The risk stratification table provided by the NCCN, which includes cytogenetic and molecular abnormalities, is featured in Table 2. Within each of the risk classes, the presence or absence of minimal residual disease (MRD) may add independently to prognosis, with patients with unfavorable risk disease appearing to benefit the least from MRD-guided therapy (Rubnitz et al., 2010). However, MRD is still being evaluated in prospective studies and the NCCN does not yet recommend its use for treatment planning (NCCN, 2019).

THE NEW MANAGEMENT PARADIGM

Understanding of AML has become more complex with the development of NGS, understanding of chromosomal abnormalities, and assessing flow cytometry for minimal residual disease. Risk stratification and treatment plans have been developed by the NCCN Guidelines (2019). Until recently, treatment advances had been nonexistent for almost the past 30 years. Acute myeloid leukemia treatment has a history of multiple drug failures in an ever-changing landscape of disease understanding. However, during recent years, there has been robust characterization of molecular targets for drug development, leading to the U.S. Food & Drug Administration (FDA) approval of eight new treatments during 2017 and 2018 (Perl, 2017; Saygin & Carraway, 2017). Additionally, there have been advances in how to use these agents in risk-adapted management plans, with improvement in OS and event-free survival.

Given these advances, oncology clinicians are challenged to continually evaluate and implement evolving guidelines (Döhner, Weisdorf, & Bloomfield, 2015) and changes in practice. Among these clinicians are advanced practice providers (APPs), a group that includes physician assistants (PAs), nurse practitioners (NPs), clinical nurse specialists (CNSs), and oncology pharmacists, who have become integral members of the oncology care team (Bruinooge et al., 2018; Kirkwood et al., 2018). To provide optimal care for patients with AML, clinicians must be able to interpret the clinical data supporting the safe and effective use of currently approved agents and integrate available therapeutics into risk-adapted, comprehensive management plans. Advanced practice providers must be prepared to assess treatment response and address treatment-related adverse events, as they are often the clinicians patients see most of-

Table 2. Risk Stratification Based on Cytogenetics and Molecular Abnormalities

Risk status	Cytogenetics	Molecular abnormalities
Favorable risk	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*	Biallelic mutated *CEBPA*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}
Intermediate risk	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*	Mutated *NPM1* and *FLT3*-ITD^{high}
	Others not classified as favorable or adverse	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse-risk genetic lesions)
Poor risk	t(6;9)(p23;q34.1); *DEK-NUP214*	Wild-type *NPM1* and *FLT3*-ITD^{high}
	t(v;11q23.3); *KMT2A* rearranged	Mutated *RUNX1*
	t(9;22)(q34.1;q11.2); *BCR-ABL1*	Mutated *ASXL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*	Mutated *TP53*
	-5 or del(5q); -7; -17/abn(17p)	
	Complex karyotype; monosomal karyotype	

Note. Information from NCCN (2019).

ten. They must also be aware of the significance of emerging agents and ongoing clinical trials that may benefit this high-risk disease group. ●

Disclosure

Dr. Nix has served on the speakers bureau for Coherus BioSciences and advisory boards for Bristol-Myers Squibb, Genentech, Puma, Sandoz, and Teva. Ms. Price has served as a consultant for Agios and on an advisory board for Daiichi Sankyo.

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