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Advances in Genomic Profiling and Risk Stratification in Acute Myeloid Leukemia

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Abstract

Objective: To review the current state of molecular and genetic profiling of acute myeloid leukemia (AML) and its implications.

Data Source: Peer-reviewed journal articles.

Conclusion: Significant advances in the understanding of the pathology of acute myeloid leukemia have led to refined risk stratification of patients and application of novel targeted therapies based on genetic profiles. Minimal residual disease testing allows for highly sensitive disease surveillance that can be used to predict relapse and assess treatment response.

Implications for Nursing Practice: Accurate prognostication and therapeutic decision-making for patients with acute myeloid leukemia is dependent on molecular profiling. Being knowledgeable of the implications of minimal residual disease testing is critical for patient-centered care.

Keywords

acute myeloid leukemia (AML); genetics; mutations; prognosis; minimal residual disease (MRD); molecular targeted therapies

Introduction

Case

A 67-year-old woman with hypertension and diabetes presents with several weeks of fatigue and epistaxis and is diagnosed with acute myeloid leukemia (AML). Standard work-up revealed a normal karyotype and mutations in *NPM1*, *FLT3*-ITD with a high allelic ratio, and *IDH2*. How does the genetic profiling of this patient influence clinical management, including risk stratification, prognosis, induction and consolidation chemotherapy, disease response, and further treatment options? *NPM1* mutation, as discussed further, is a favorable

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risk mutation, while *FLT3*-ITD with a high allelic ratio represents an adverse risk marker. Concomitant NPM1 and FLT3-ITD mutation with a high allelic ratio is considered intermediate risk. Standard '7 +3' (cytarabine continuous infusion + anthracycline) with either midostaurin, a tyrosine kinase FLT3 inhibitor, or gemtuzumab ozogamicin (GO), an antibody drug conjugate targeting CD33, may be considered during induction because of her risk profile. The *NPM1* mutation will allow for highly specific surveillance of her disease and monitoring of treatment response following induction and consolidation therapy through minimal residual disease (MRD) testing. Further, although allogeneic stem cell transplant is not standardly considered for patients with *NPM1* without a *FLT3* mutation; transplant is often considered in patients with co-occurring *NPM1* and *FLT3* given the relatively high risk of relapse in patients with *FLT3*-ITD mutations. Lastly, because her AML harbors an *IDH2* mutation, she may respond well to venetoclax, a small-molecule inhibitor of apoptosis regulator, BCL-2, and may garner benefit from a targeted *IDH2* inhibitor on relapse.

AML is a heterogenous hematologic malignancy driven primarily by genetic abnormalities in myeloid progenitor cells causing an accumulation of abnormal immature blasts in the bone marrow.[1] These leukemic cells impair normal hematopoiesis and eventually cause bone marrow failure, leading to characteristic clinical symptoms such as fatigue, infection, and bleeding. The diagnosis is made through a bone marrow biopsy, which identifies an elevated proportion of blasts within the marrow. Morphology, immunophenotyping, cytogenetic analysis, and molecular analysis lead to a further refinement of the diagnosis.[2]

Risk Stratification

Traditionally, risk stratification in AML was based on the morphology of the leukemic cells, cytogenetic abnormalities, and clinical features.[3] However, more recently molecular profiling has allowed for the further classification of AML into prognostically distinct subgroups.[4] Updated 2016 World Health Organization guidelines include the category "AML with recurrent genetic abnormalities," which sub-classifies AML by many known molecular and genetic abnormalities.[5] Furthermore, the 2017 European Leukemia Net (ELN) guidelines revised their risk stratification to include both cytogenetics and genomic information to stratify patients into one of three prognostic risk groups: favorable, intermediate, or adverse risk (Table 1).[6] Other well-established risk-stratification models including the Southwest Oncology Group classification[7] and the AML composite model,[8] variably utilize cytogenetic and molecular abnormalities to define risk. The National Comprehensive Cancer Network, which is a consortium of National Cancer Institute-designated comprehensive centers that produce expert-consensus clinical guidance documents, has adopted the ELN guidelines for risk stratification.[9] The World Health Organization, ELN, and National Comprehensive Cancer Network convene regularly to update clinical recommendations and diagnostic criteria.[9]

The initial intention for developing genetic risk categories by the ELN was to standardize the reporting of molecular abnormalities that have been shown to correlate with clinical outcomes.[6] Principally, these risk categories are used to inform prognosis, including overall survival, disease-free survival, chance of obtaining complete remission (CR), and risk of relapse. Mrozek et al[10,11] illustrate the substantial prognostic differences between genetic

risk categories. For example, among patients <60 years of age, 60% with favorable-risk disease were alive at 5 years, as compared with only 10% of those with adverse-risk disease, highlighting the importance of allocating patients into prognostic risk groups at diagnosis. For older patients (≥60 years), overall outcomes are significantly worse because of a higher probability of treatment-related mortality with conventional induction chemotherapy, increased incidence of AML from pre-existing myeloid neoplasms, and a more chemoresistant disease biology; 2-year overall survival is 40% for favorable risk and <10% for adverse risk.[10]

The Development of Molecular and Genetic Profiling

As illustrated earlier, identifying individual mutations within genes can drastically change overall risk. For example, patients with a normal karyotype who are found to have an *NPM1* mutation without mutations in *FLT3*-ITD are considered favorable risk by ELN and achieve complete response rates between 80% and 90%, whereas those with an *NPM1* mutation and a *FLT3*-ITD mutation with a high allelic ratio, as in the case presented earlier, have CR rates of 40% to 60%.[4,12]

Over the last decade there has been increasing interest in further subclassifying AML into prognostic risk categories. Papaemmanuil et al[13] presented the results of the largest mutational analysis performed in AML (>1,500 patients) to illustrate how genomic classification, specifically the identification of driver mutations (those mutations that cause the pathologic effects) can influence prognosis. These results highlight important progress in the development of an integrated risk stratification system aimed at delineating risk to inform clinical practice. Papaemmanuil et al[13] proposed a new classification system based on genetic subgroups (Table 2).

More recently, the entire composite landscape of the molecular abnormalities of AML has been explored. We now have a deeper understanding of the key genetic determinants of disease and the clonal nature by which these mutations occur.[14] In whole genome sequencing analysis of 200 patients, 23 genes were identified to be commonly mutated in AML.[15] Most patients were found to have ≥ two acquired mutations.[15] *NPM1*, a nuclear-shuttling factor, is mutated in roughly 20% to 30% of patients and is the most common mutation seen in AML. Mutations are also common in activated signaling including mutations in *FLT3-ITD*, *FLT3-TKD*, *NRAS*, and *KRAS*.[14] Other commonly mutated genes are those that lead to aberrant regulation of DNA methylation and hydroxymethylation (*DNMT3A, TET2*, *IDH1, IDH2*), those that involve messenger RNA splicing (*SF3B1*, *SRSF2*), those that cause modified chromatin architecture (*ASXL1*, *EZH2*), and those that lead to deregulation of transcription (*RUNX1*, *CEBPA*, and *WT1*). Mutations in *TP53*, a tumor suppressor gene, are also common (6%).[16]

Because of the increasing awareness of the prognostic and clinical importance of genetic abnormalities in AML, mutational analysis has been integrated into the diagnostic work-up of newly diagnosed patients.[17] Next-generation sequencing that is able to identify specific genetic mutations within a relatively short period of time has become the standard of care for classifying mutations for diagnostic purposes. Next-generation sequencing panels

can precisely identify multiple gene mutations that occur concomitantly, which is critical for diagnostic purposes. In addition to identifying individual mutations, next-generation sequencing also allows for the quantification of mutational burden by estimating proportions of cells carrying a mutation based on the allelic frequency.[15] Identifying high versus low allelic burden is currently important for proper risk stratification of *FLT3-ITD* AML.[6] Prognostic implications of allelic burden for other subtypes of AML and myelodysplastic syndromes are being explored.[18]

Mutations with Clear Clinical Impact

In general, while hope remains that a deepening understanding of the molecular basis of disease will lead to transformative single-agent targeted therapies, as seen in chronic myeloid leukemia and acute promyelocytic leukemia, many mutational signatures largely only have prognostic and not therapeutic implications.[19] However, several specific genetic alterations have clear clinical implications (outlined in Table 3).[6,20]

FLT3

The FMS-like tyrosine kinase 3 (*FLT3*) gene is important for proliferation and survival of early hematopoietic cells. Mutations within *FLT3* are commonly classified as internal tandem duplication (ITD) or tyrosine kinase domain (TKD) mutations.[21] *FLT3*-ITD mutations occur in 20% of patients with AML and TKD in 10%.[22] Both mutations lead to uncontrolled proliferation of leukemic cells. *FLT3*-ITD is associated with inferior outcomes, whereas *FLT3*-TKD is thought to be prognostically neutral.[22] A higher burden of mutations is associated with less favorable outcomes.[21] ELN risk classification stratifies *FLT3*-ITD mutations by high and low allelic ratio, with a high ratio being classified as adverse risk if not accompanied by an *NPM1* mutation.[6]

Several agents have been developed specifically to target the *FLT3* mutation, including first-generation (midostaurin, lestaurtinib, sunitinib, sorafenib) and second-generation (gilteritinib, quizartinib, crenolanib) *FLT3* tyrosine kinase inhibitors.[20] The overall benefit of such agents has been modest. Midostaurin, when used with traditional induction and consolidation chemotherapy, was shown to improve progression-free and overall survival (hazard ratio for death 0.78; confidence interval 0.63–0.96; $P = .009$) for all patients with *FLT3* mutations and is now considered a standard-of-care agent to include in induction with 7+3 and consolidation regimens (with high-dose cytarabine) for patients age 18 to 60 years.[23] Sorafenib has been shown to have modest benefits for *FLT3*-ITD patients when used prior to or after allogeneic hematopoietic cell transplant (allo-HCT).[24] Gilteritinib was recently approved by the US Food and Drug Administration for the treatment of patients with relapsed or refractory disease based on the results of the randomized phase 3 ADMIRAL trial, which showed a combined CR and CR with incomplete hematologic recovery of 30%, with an additional 10% achieving a partial remission, for an overall response rate of 40% (confidence interval 34%–47%).[25] Median overall survival in the trial was 9.3 months. Quizartinib, another FLT3 inhibitor currently under investigation, has shown promise in the management of relapsed/refractory AML with FLT3-ITD mutations. The QUANTUM-R randomized phase 3 trial of quizartinib versus physician choice

significantly prolonged survival (6.2 months *v* 4.7 months).[26] Further, randomized phase 3 trials are investigating crenolanib in newly diagnosed and relapsed/refractory AML though the results have yet to be reported. In general, patients with *FLT3*-ITD mutations commonly respond poorly to standard chemotherapy regimens and often allo-HCT is considered for eligible patients.[27]

NPM1

Encompassing nearly 30% of AML with normal cytogenetics, AML with mutated *NPM1* is generally considered to be favorable-risk.[6] *NPM1* is uncommonly found in patients with myelodysplastic syndromes or other leukemias.[28] Patients with *NPM1*-mutated AML are frequently younger and often harbor characteristic co-occurring mutations in DNA hydroxymethylation genes (such as *DNMT3A*, *TET2*, *IDH1*, and *IDH2*), which are found in nearly 75% of patients. Prognosis of patients with *NPM1* has been shown to vary significantly by co-occurring mutations. Co-mutations in *RAD21* and/or *NRAS* codon 12/13 confer extremely favorable outcomes, whereas co-mutations in *DNMT3A* and *FLT3*-ITD with a high allelic ratio confer inferior outcomes.[14] Patients with *NPM1* mutations without *FLT3* mutations or with *FLT3*-ITD with a low allelic ratio had a median overall survival of 79.7 months, while those with *FLT3*-ITD with a high allelic ratio had a median overall survival of only 17.2 months. This demonstrates the importance of the overall mutational spectrum when prognosticating outcomes in AML.[29]

Patients with *NPM1* mutations without adverse features typically have a favorable response to conventional induction chemotherapy. The well-preserved unique DNA signature of *NPM1* mutations allows clinicians to utilize copy number of transcripts for clinical surveillance and measurement of response through MRD testing, which is discussed later in this article. GO has been shown to improve EFS in patients 50 to 70 years of age with intermediate- and favorable-risk disease, and is often considered in patients with *NPM1* mutations despite not having an established survival benefit.[30] GO has been shown to produce deeper responses and improved MRD when added to traditional induction regimens.[31] Allo-HCT is typically not considered in first CR given the high probability of long-term disease-free survival with chemotherapy alone in these favorable-risk patients. However, a higher rate of relapse is seen in those with suboptimal clearance of *NPM1* transcripts by MRD testing and often necessitates consideration of allo-HCT in eligible patients.[32]

IDH1 and IDH2

Isocitrate dehydrogenases (IDHs) are a class of enzyme catalysts that are found in the cytoplasm, peroxisome, and mitochondria of human cells. Mutations in *IDH1* and *IDH2* have been described in colorectal cancer, glioblastoma, oligodendrogliomas, and more recently in AML.[33] Approximately 16% of patients with AML harbor a mutation in either *IDH1* or *IDH2*.[34] There is no consensus on their prognostic value and, therefore, they are not included in current risk-stratification models.[6]

IDH-mutation status has several clinical implications. Ivosidenib, a small-molecule inhibitor of mutant *IDH1*, was shown to be safe and tolerable in patients with relapsed or refractory

IDH1-mutated AML, with overall response rates equal to approximately 42%, and is now approved by the US Food and Drug Administration for the treatment of newly diagnosed, untreated elderly patients with AML (≥75 years or who have comorbidities that preclude intensive chemotherapy) with an *IDH1* mutation.[35] Enasidenib, an *IDH2* inhibitor, was also shown to be safe and tolerable when given to patients with relapsed or refractory *IDH2*-mutated AML, with response rates similar to ivosidenib in IDH-1 mutated –AML (approximately 40%).[36] IDH inhibitors produce differentiation of leukemic cells into mature neutrophils, and, if this differentiation occurs rapidly, can lead to differentiation syndrome, a potentially lethal clinical combination of several clinical signs and symptoms, including hypoxia, fever, pleural effusion, rash, pain, and potentially disseminated intravascular coagulopathy. Approximately 12% of patients treated with enasidenib develop differentiation syndrome.[37] Treatment requires the urgent use of corticosteroids. *IDH1* and *IDH2* have also been shown to induce dependence of AML cells to *BCL*-2, an anti-apoptotic gene.[38] This dependence may confer increased sensitivity to the *BCL*-2 targeted agent, venetoclax, when used with hypomethylating agents.[39]

TP53

Mutations in the *TP53* gene are identified in over one half of human cancers.[40] *TP53* is a tumor suppressor gene, functioning to maintain genomic stability following DNA damage, activating DNA repair and limiting cellular proliferation. It is mutated in roughly 8% of patients with de novo AML and may be higher in those with secondary AML.[41] It commonly occurs in patients with a complex (defined as three or more cytogenetic abnormalities) and monosomal karyotype (defined as loss of two or more autosomal chromosomes or a single autosomy monosomy in presence of structural abnormalities).[5,13,42] Patients with AML and *TP53* mutations also tend to be older.[43] A *TP53* mutation portends a very poor prognosis compared with those without such mutations, with inferior overall survival in both patients under age 60 years (median, 10.7 months *v* not reached) and those older (median, 6.0 months *v* 14.7 months).[41] For patients with a complex karyotype, *TP53* mutation is the most important prognostic factor.[43]

The dismal prognosis is thought to be because of the impaired susceptibility of mutated blasts to DNA-damaging agents, leading to inferior responses to traditional chemotherapy.[40,43] Because of this, there has been an attempt to evaluate the response of patients with *TP53* mutations to non-traditional agents. Hypomethylating agents have been shown to be effective in patients with *TP53* mutations with and without the BCL-2 inhibitor venetoclax.[39,44] These agents are attractive for use in older patients with *TP53*-mutated AML; however, overall prognosis remains very poor. Despite significant effort and resources expended across multiple cancer types, targeted agents for *TP53* have been disappointing.[45] Although allo-HCT has been shown to be advantageous for many patients with adverse-risk disease, the outcomes following transplant for those with *TP53* mutations and complex karyotype (88% of patients with a *TP53* mutation) remain poor.[46]

Core Binding Factor (CBF)

This subset of AML includes patients with chromosomal abnormalities t(8;21) or inv(16)/t(16;16) corresponding to the *RUNX1-RUNX1T1* or *CBFB-MYH11* fusion genes.[47] These

chromosomal abnormalities result in abnormal transcription of genes, resulting in the loss of function of the core binding complex that is involved in normal hematopoiesis.[48] Prognosis of patients with CBF-AML is traditionally favorable; however, co-occurring mutations in *KIT* may portend a worse prognosis.[47]

Patients with CBF-AML typically respond well to standard chemotherapy regimens.[13] The clinical management of patients with CBF-AML is similar to those with *NPM1*, where GO has been shown to be beneficial in induction regimens.[49] Those with inv(16)/t(16;16) have a 5-year overall survival rate between 60% and 80%. Five-year overall survival for those with t(8;21) is approximately 50%. Allo-HCT is typically not considered in the first CR for patients with favorable-risk disease, such as CBF-AML. For patients with CBF-AML with *KIT* mutations or overexpression of the KIT receptor, dasatinib, a multi-tyrosine kinase inhibitor that strongly inhibits KIT, may provide benefit.[50]

Minimal Residual Testing

Many patients achieve CR by morphology following induction chemotherapy; however, relapse remains common and leads to the majority of morbidity and mortality in AML. Technical advances in quantitative real-time polymerase chain reaction (PCR) and flow cytometry have enabled progressively improved sensitivity in the detection of leukemic cells. The detection of MRD in patients in CR illustrates that a residual reservoir of cells is likely driving relapse.[51]

Several techniques can be used for MRD testing with variable sensitivity and standardization. Standard MRD testing platforms include multi-parameter flow cytometry (MFC) and PCR. MFC-MRD tests rely on the identification of a unique antigen phenotype of the leukemia cells that differs significantly from the typical antigen-expression pattern of normal or regenerating cells. Such unique immunopheno-types are identifiable in the majority of patients and can be used to follow response to treatment. There are limitations to this approach, including variable sensitivity in detection, change in phenotype over time, lack of standardization across centers, and reliance on the expertise of the MFC analyst.[52] Sensitivity to detect leukemic cells by MFC-MRD is typically between one in 1,000 to one in 10,000.[53]

Real-time PCR is able to detect the presence of abnormal mRNA transcripts produced by leukemic cells. This technology has been clinically implemented in the monitoring of *BCR*/*ABL* transcripts in CML and *PML*/*RARA* transcripts in acute promyelocytic leukemia and is increasingly being used in MRD testing for AML. CBF-AML and mutated *NPM1*-AML are commonly monitored through PCR.[31] Although sensitivity varies by assay, typically PCR has a better sensitivity than MFC-MRD, with the ability to detect one in 10,000 to one in 100,000 cells. Limitations to PCR testing include lack of availability for many AML subtypes and the potential for false-positive results. Identifying a more ubiquitously expressed aberrant transcript in AML, such as *WT1*, may allow for PCR testing to be used across subtypes.[54]

MRD testing is typically used clinically in two settings: determination of response to initial therapy and as a tool to predict relapse.[53] Detection of MRD provides important prognostic information regarding the depth of initial response to induction therapy. Many studies have illustrated that residual disease, as detected by MRD techniques following induction chemotherapy, confers significantly higher relapse risk and inferior overall survival.[53,55] Further work remains to standardize both timepoints following therapy to assess MRD and therapeutic interventions following the detection of MRD. Intensifying therapy, including additional chemotherapy or immunotherapy through HCT, is often suggested, though randomized trials illustrating the benefit of MRD-directed therapy are currently lacking.[56]

Implications for Nursing Practice

The expansion of the therapeutic landscape and advances in risk stratification based on genetic profiling have changed practice in AML with implications for nursing practice. Whereas previously patients were started on chemotherapy fairly quickly following initial diagnosis, treatment decisions now are dependent on specialized genetic testing to identify targeted agents and appropriately assess risk. This often necessitates a several-day delay from initial diagnosis to induction chemotherapy, during which time cytoreductive agents such as hydroxyurea are often administered by nurses. Further, with the advent of targeted therapies with more tolerable side effects, patients often have additional therapeutic options, even at relapse. Even for patients with significant comorbidities or advanced age whose disease has progressed through first-line agents such as azacytidine or decitabine, targeted therapy may offer an opportunity to prolong survival and maintain quality of life. Certainly, enrollment in a clinical trial should be considered for such patients given the poor outcomes even with targeted therapy. Lastly, the development of MRD testing has allowed for a more dynamic assessment of individual prognosis. Treatment decisions, such as if patients should be considered for allo-HCT, now often depend on MRD status in addition to baseline risk. Oncology nurses are integral in understanding the impact of genetic profiling and risk stratification in adults with AML and the impact it will have on symptom management and the patients' well-being.

Future directions

Given the rather nascent development of genetic profiling in AML to predict risk, further refinement of risk-prediction models is expected. Studies illustrating the prognostic importance of individual genes such as *IDH1*, *IDH2*, *SRSF2*, and c-*KIT*, as well as the influence of combinations of genes, will continue to be important. Further, while current clinical risk-stratification models use information that is easily accessible through standard-of-care techniques, novel application of emerging technology may better delineate risk.[57] Gene expression profiles, which provide a functional view of the protein expression of leukemic cells, have been associated with prognosis, though are not currently integrated clinically.[58] Using gene expression profiles to predict response to individual therapies is now becoming possible and may inform choice of induction therapy.[59] Use of micro RNAs, immune polymorphisms, and epigenetic profiles for risk stratification is also promising.[60–63] Whereas most of these prognostic models use a baseline risk assessment to guide clinical

decision-making, dynamic models that integrate response to therapy likely assessed through MRD testing have the potential to vastly improve prognostication for individual patients.[57]

Conclusion

Significant advances in the genetic profiling of AML have led to a better understanding of individual risk stratification. Treatment decisions in AML are infrequently straightforward and should be tailored to the individual preferences of patients to trade-off risks to obtain benefits. A clear understanding of the risks and benefits of therapy, especially the overall prognosis, is vital, therefore, to determine the overall goals of therapy. These goals will inform the intensity of therapy and often the specific chemotherapeutic agent chosen through a process of shared decision-making between patients and clinicians. As we advance in our understanding of individualized prognosis through the further refinement of risk-stratification models, we will be better equipped to practice patient-centered care.

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Table 1

2017 ELN AML risk stratification by genetics.[6]

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

*Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5).

†The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

‡Three or more unrelated chromosome abnormalities in the absence of one of the World Health Organization-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.

§Defined by the presence of one single monosomy (excluding loss of X or Y) in association with at least one additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).

#These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

Table 2

Proposed genomic classification of AML.[13]

Suggested genomic subgroup	Commonly mutated genes
AML with NPM1 mutation	*NPM1, DNMT3A, FLT3*^{ITD}*, NRAS, TET2, PTPN11*
AML with mutated chromatin, RNA-splicing genes, or both	*RUNX1, MLL, SRSF2, ASXL1*
AML with TP53 mutations, chromosomal aneuploidy, or both	*TP53*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);	*NRAS, CBF*
AML with biallelic CEBPA mutations	*CEBPA, NRAS, WT1, GATA2*
AMLwith t(15;17)(q22;q12); PML–RARA	*FLT3*^{ITD}*, WT1*
AML with t(8;21)(q22;q22); RUNX1–RUNX1T1	*KIT*
AML with MLL fusion genes; t(x;11)(x;q23)	*NRAS*
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); GATA2, MECOM(EVI1)	*KRAS, NRAS, PTPN11, ETV6, PHF6, SF3B1*
AML with IDH2R172 mutations and no other class-defining lesions	*IDH2, DNMT3A*
AML with t(6;9)(p23;q34); DEK–NUP214	*FLT3*^{ITD}*, KRAS*
AML with driver mutations but no detected class-defining	*FLT3*^{ITD}*, DNMT3A*
AML with no detected driver mutations	
AML meeting criteria for ≥2 genomic subgroups	

Table 3

Frequency and clinical implications of individual genetic abnormalities.[6,20]

Genetic abnormality	Incidence (of all AML patients)	Influence on prognosis	Therapy implication
FLT3-ITD	20%−25%	Adverse if high allelic ratio (without *NPM1*)	Consider midostaurin with induction
			Consider gilteritinib on relapse or if refractory
			Consider allo-HCT if eligible in first CR
			Consider sorafenib or gilteritinib following allo-HCT
NPM1	20%−30%	Favorable (without *FLT3*-ITD^{high})	Consider GO with induction (50–70 years old)
			Treatment course informed by clearance of *NPM1* transcripts
IDH1 and *IDH2*	15%−20% (combined, 8%−10%, respectively)	Unclear	Consider ivosidenib/enasidenib in relapse
			May respond well to venetoclax with HMA
TP53	5%−10%	Adverse	Consider HMA ± venetoclax

Abbreviations: Allo-HCT, allogeneic hematopoietic cell transplant; CR, complete remission; GO, gemtuzumab ozogamicin; HMA, hypomethylating agent.