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Title: Navigating through Mutations in Acute Myeloid Leukemia. What Do We Know and What Do We Do with It?

Running Head: Mutations in AML

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Abstract

Acute myeloid leukemia (AML) is a clonal hematopoietic disease characterized by abnormal proliferation of early precursors of myeloid cells and blasts. AML represents a heterogeneous disease group with a significantly complex biology and pathophysiology. Various translocations, chromosome copy number changes and mutations have been described in AML, some of which help define the diagnosis, prognosis and management. The optimal treatment in most cases remains cytarabine and anthracycline-based combination regimens followed by the allogeneic stem cell transplant. However, older age and decreased tolerance to conventional therapies pose a major challenge for the conventional therapies which has lead to the development of effective and less toxic therapy modalities as reviewed in this manuscript.

Keywords: AML, mutations, cytogenetics, targeted therapies

INTRODUCTION

Acute myeloid leukemia (AML) represents a group of diseases characterized by clonal expansion of myeloid blasts in peripheral blood, bone marrow, other organs and cavities. The worldwide incidence of AML is 2.5-3 cases per 100,000 population annually and reportedly most common in the Western World (1). A diagnosis of AML can be made based on 1) ≥20% blasts of myeloid and/or monocytic or megakaryocytic lineages and 2) presence of recurrent cytogenetic abnormalities including t(8;21) (q22;q22.1), inv16 (p13.1q22) or t(16;16) (p13.1:q22) and *PML-RARA* fusion (1). AML can arise *de novo* or evolve from myelodysplastic syndromes (MDS) and/or myeloproliferative neoplasms (MPN). The

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current risk stratification for AML is primarily based on cytogenetics and molecular genetic abnormalities (Table 1) according to the European Leukemia Net (2). Recent developments in the molecular biology of this clinically, morphologically and phenotypically heterogeneous disease lead us to a more comprehensive diagnostic approach, including conventional karyotyping, fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR) and next generation DNA sequencing (NGS), enable us to predict prognosis in these patients and develop of more effective targeted treatments. NGS is a fairly novel technology that massively parallels or deep sequences the DNA, allowing us to sequence the entire human genome within a day (3). Detection of somatic mutations by NGS in AML cases using large multi-gene panels provides important information that can be used in diagnosis, prognostic risk stratification, evaluation for targeted treatments, and monitoring for minimal residual disease (MRD).

Mutations in AML and Clinical Consequences

In AML, the transcription-factor fusions [e.g. t (8;21), inv(16) and t(15;17)] are the first identified genomic alteration and have been linked to disease initiation (4, 5). A recent whole genome sequencing study on 200 adult de novo AML patients published by The Cancer Genome Atlas (TCGA) Research Network classified AML associated mutations in functional categories (Table 2) according to the results of this comprehensive analysis (6). This data suggests that one mutation in any of these pathways is sufficient for pathogenesis of AML and certain mutations that are common in AML (e.g., in DNMT3A, NPM1, CEPBA, IDH1/2, and RUNX1) to play a role in the initiation of AML similar to the fusion genes.

In addition to the role in the pathogenesis of AML, these mutations appear to have clinical utility in prognostication, determining the therapy options and detecting MRD. Recently approved and under investigation agents targeting these mutations are summarized in Table 3.

FLT3 mutation: Mutations involving *FLT3* gene, a member of the class II tyrosine kinase receptor, has been extensively studied and shown to play a crucial role in AML promoting expansion of hematopoietic precursors (7). *FLT3* is not uncommonly expressed in AML blasts and is associated with poor prognosis. FLT3 internal tandem duplication (*FLT3*-ITD) mutations result in increased tyrosine kinase activity and are the first mutations reported that have a prognostic impact in AML (8). Subsequent large cohort studies as well as sporadic case reports demonstrate the association between *FLT3*-ITD mutations and an increased relapse rate as well as decreased overall survival (9-11). Point mutations occurring in the *FLT3* gene in the constitutive activation of the kinase domain are known as *FLT3*-TKD mutations. Both *FLT3*-ITD and *FLT3*-TKD mutations occur in AML with normal karyotype (~35% and 10%, respectively) as well as AML with recurrent cytogenetics (12). *FLT3* mutation analysis was historically performed for prognostication in AML; however, with the advances in *FLT3*-inhibitors, it now clear that it has prognostic and predictive value.

NPM1 mutation: Nucleaophosmin (NPM) is a protein that is important in a wide-spectrum of cell processes including cell proliferation, DNA repair and genome stability (13). Frameshift mutations of the *NPM1* gene are observed in one third of adult patients with *de novo* AML; WHO classifies AML with *NPM1* mutation as a separate entity (13). *NPM1* mutations are associated with a favorable prognosis in AML with normal karyotype without other mutations. AML with mutated *NPM1* commonly harbors other mutations involving the *FLT3* gene (in 40-50% of patients), *DNMT3A, TET2, IDH1,* and, *IDH2* (14). A recent large retrospective study performed by Ostronoff et al., showed that AML patients ages 55 to 65 years and *NPM1+/FLT3*-ITD+ have an improved survival when compared to the group without this phenotype (15). Mason et al. studied 133 cases with *NPM1* mutated AML; 40% of these cases demonstrated an APL-like phenotype with lack of CD34 and HLA-DR expression (14) suggesting a

maturation arrest of myeloid differentiation, closer to the promyelocytic stage. Furthermore, these APL-like cases also showed *TET2, IDH1,* or *IDH2* mutations with a superior outcome and lower frequency of *DNMT3A* mutations. The results of this study were interesting and indicated a potential use of ATRA and ATO in the cases of AML with mutated *NPM1* and APL-like phenotype.

CEBPA mutation: *CEBPA,* a transcription factor in hematopoietic stem cells, is responsible for the differentiation to the myeloid progenitors and functions as promoter for myeloid and monocytic differentiation (16). *CEBPA* is expressed in granulocytes, monocytes and eosinophils. *CEBPA* mutations occur in approximately 10% of AML cases and double mutations confer a favorable diagnosis (16, 17). However, when single mutation of *CEBPA* occurs, other concurrent mutations, including *NPM1* and *FLT3*-ITD affect the outcome in these cases (18).

Other mutations not uncommonly detected in AML include *DNMT3A, IDH1* and *IDH2, RUNX1, ASXL1, TP53, KIT,* and *TET2.*

DNMT3A mutation: *DNMT* genes play a role in methylation of CpG islands and reduce the expression of downstream genes resulting in genome instability and cancer (19). *DNMT3A* mutations occur in 18%-22% of AML cases and one third of AML cases with normal cytogenetics (20-23). Studies showed that *DNMT3A* mutations are often accompanied by other mutations including *FLT3, NPM1*, and *IDH1* and *IDH2* mutations (24) and confer an unfavorable prognosis in both younger and older patients (17). Treatment with high dose daunorubicin (25) and hematopoietic stem cell transplant (19) have been shown to increase the overall survival in AML patients with *DNMT3A* mutation.

IDH1 and IDH2 mutation: IDH is an essential enzyme in cell metabolism and gain of function mutations in IDH lead to DNA methylation and impaired myeloid differentiation (26). Approximately 20% of all AML

and 30% of AML with normal karyotype cases harbor *IDH1* or *IDH2* mutations (27). *IDH1* mutations have been shown to confer an overall unfavorable prognosis in AML with shorter OS and event-free survival, while the impact of mutations of *IDH2* mutation differs based on type of mutation: $IDH2^{R140}$ are associated with a better prognosis in younger AML patients whereas $IDH2^{R172}$ is associated with a poorer outcome (28, 29). *IDH1/IDH2* small inhibitor molecules are available in treatment of AML.

RUNX1 mutation: AML with *RUNX1* is a relatively infrequent provisional AML entity. *RUNX1* mutation frequency increased with age: 5%-10% in patients <60 years and 10-20% ≥60 years. It is more frequent in men than women and is often associated with secondary AML evolving from MDS, failure of induction therapy and inferior OS (30).

ASXL1 mutation: *ASXL1* mutations are detected in approximately 10% of all *de novo* AML cases and frequency increases significantly with age, particularly in patients more than 60 years old. *ASXL1* mutation in AML constitutes an inferior outcome with low complete remission rates.

TP53 mutation: p53 is a tumor suppressor transcription factor that is actively involved in hematopoietic stem cell quiescence and self-renewal preventing leukomogenesis (31). *TP53* mutations in AML have recently been the focus of investigations. *TP53* mutations occur in 8% of de novo AML and are early leukomogenic initiating driver mutations resulting in an aggressive disease course, therapy-resistance and poor outcome even after allogeneic HSCT (32). MDM2 inhibitors appear to be promising in targeting mutant p53 in AML treatment, although the therapeutic progress is still inadequate.

KIT mutation: *KIT* mutation is found in 13%-46% of core-binding protein factor (CBF) AML including t(8;21)(q22;q22) and inv(16)(p13;q22) (33). While CBF-AML is generally considered to be in the

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favorable risk group, co-existence of *KIT* mutation is associated with unfavorable prognosis. Targeted tyrosine kinase inhibition of *KIT* is still in development.

TET2 mutation: Somatic methylcytosine dioxygenase 'ten–eleven translocation 2' (TET2) mutations occur in approximately 23% of AML (34). *TET2* mutation is a common finding among the elderly population with clonal hematopoiesis. *TET2* is often associated with AML with normal karyotype and NPM1 mutation (30).

CONCLUSION

AML is the most common acute leukemia in the adult population with a complex biology and significant heterogeneity. Over the last few decades, many balanced and unbalanced chromosomal abnormalities and mutation have been described that are used to diagnose and also prognosticate the disease. Despite the advances in molecular pathogenesis and targeted drug discoveries, the overall long-term survival in the majority of the patients remains poor. The advanced age of onset and exclusion of optimal cytotoxic treatments in the elderly patient group due to increased complications and decreased tolerance makes the treatment of AML using conventional therapies challenging. Several targeted therapies, i.e. *FLT3*-inhibitors, have been introduced for AML. However, the molecular heterogeneity of the disease and co-existing mutations and translocations makes single-targeted-therapy option less likely to succeed. Further understanding of the complex biology of AML and identification of the optimal targeted treatments will benefit particularly patients of older age as well as patients with complex karyotype and refractory disease.

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Table 1. Risk stratification for AML according to the European LeukemiaNet (2)

Genetic Group	Subsets
Favorable	t(8;21)(q22;q22); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Mutated NPM1 without FLT3-ITD (normal karyotype) Mutated CEBPA (normal karyotype)
Intermediate-I	Mutated NPM1 and FLT3-ITD (normal karyotype) Wild-type NPM1 and FLT3-ITD (normal karyotype) Wild-type NPM1 without FLT3-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); MLLT3-MLL Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1 t(6;9)(p23;q34); DEK-NUP214 t(v;11)(v;q23); MLL rearranged -5 or del(5q); -7; abnl(17p); complex karyotype*

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* Complex karyotype is defined by three or more chromosome abnormalities in the absence of designated recurrent translocations or inversions by the WHO.

Table 2. Functional gene groups in AML according to the The Cancer Genome Atlas Research Network (6)

Functional gene group	Genes in the group
Spliceosome	*CSTF2T, DDX1, DDX23, DHX32, HNRNPK, METTL3, PLRG1, PRPF3, PRPF8, RBMX, F3B1, SNRNP200, SRRM2, SRSF6, SUPT5H, TRA2B, U2AF1, U2AF1L4, U2AF2*
Cohesin complex	*SMC1A, SMC3, SMC5, STAG2, RAD21*
MLL-X fusions	*MLL-ELL, MLL-MLLT4, MLL-MLLT3, MLLT10-MLL*
RAS protein	*KRAS, NRAS*
Other epigenetic modifiers	*ARID4B, ASXL2, ASXL3, BRPF1, CBX5, CBX7, EED, HDAC2, HDAC3, JMJD1C, KAT6B, KDM2B, KDM3B, MLL2, MLL3, MTA2, PRDM9, PRDM16, RBBP4, SAP130, SCML2, SUDS3, SUZ12, ZBTB33, ZBTB7B, EBBPKAT6A, RPN1-MECOM, RUNX1-MECOM*

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Other Tyrosine Kinase	*ABL1, DYRK4, EPHA2, EPHA3, JAK3, MST1R, OBSCN, PDGFRB, WEE1*
Serine/Threonine Kinase	*ACVR2B, ADRBK1, AKAP13, BUB1, CPNE3, DCLK1, MAPK1, YLK2, MYO3A, NRK, PRKCG, RPS6KA6, SMG1, STK32A, STK33, STK36, TRIO, TTBK1, WNK3, WNK4*
Protein tyrosine phosphatase	*PTPN11, PTPRT, PTPN14*
Other myeloid transcription factors	*GATA2, CBFB, ETV6, ETV3, GLI1, IKZF1, MYB, MYC, MLLT10-CEP164*

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Table 3. Targeted treatments for AML, FDA-approved and under investigation agents

Target	Drug(s)	Approval status*	Indication
FLT3	Crenolanib Gilteritinib Midastaurin Quizartinib Sorafenib	Approved	New dx AML with FLT3 mutation
IDH2	Enasidenib	Approved	Adults with relapsed or refractory AML associated with IDH2 mutations.
IDH1	Ivosidenib FT-2102 and others	Approved Investigational	Adults with relapsed or refractory AML associated with IDH1 mutation
BCL2	Venetoclax	Investigational	
TET2	Vitamin C and hypomethylating agents	Approved*	AML with low blast count*
CD33	gemtuzumab ozogamicin	Approved	Newly diagnosed CD33-positive AML
MDM2	idasanutlin	Investigational	

*US Food and Drug Administration (FDA) approval status

Hypomethylating agent (Azacitidine) approved for low blast count AML in the US.

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