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A concise review on the molecular genetics of acute myeloid leukemia

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ABSTRACT

Acute myeloid leukemia (AML) is the most common acute leukemia in adults that affects the myeloid lineage. The recent advances have upgraded our understanding of the cytogenetic abnormalities and molecular mutations associated with AML that further aids in prognostication and risk stratification of the disease. Based on the highly heterogeneous nature of the disease and cytogenetic profile, AML patients can be stratified into favourable, intermediate and adverse-risk groups. The recurrent genetic alterations provide novel insights into the pathogenesis, clinical characteristics and also into the overall survival of the patients. In this review we are discussing about the cytogenetics of AML and the recurrent gene alterations such us NPM1, FLT3, CEBPA, TET-2, c-KIT, DNMT3A, IDH, RUNX1, AXSL1, WT1, Ras gene mutations etc. These gene mutations serve as important prognostic markers as well as potential therapeutic targets. AML patients respond to induction chemotherapy initially and subsequently achieve complete remission (CR), eventually most of them get relapsed.

1. Introduction

Acute myeloid leukemia (AML) is a disorder of bone marrow that results from the clonal expansion of genetically altered hematopoietic stem cells (HSCs) and hematopoietic progenitor cells in which these acquired genomic aberrations provide a selective growth advantage and impede normal hematopoiesis [1]. Present-day developments in identification of cytogenetic abnormalities and mutations have provided novel insights into the pathogenesis of AML. Apart from this, certain mutations are linked with germline predisposition and increase the risk of inherited AML, which needs family screening. Therefore, the most important steps in patient management are precise diagnosis and classification of AML [2]. In the United States it is estimated that there will be approximately 19,940 new cases of AML in 2020. AML has the highest mortality rate of all leukemias, with an estimated 11,180 deaths annually [3].

AML represents 15–20% of acute leukemia cases in children, while in adults it is about 80%. AML is the major form of leukemia in newborn and adults, but during infancy and adolescence, it represents a small fraction of cases. So it most commonly occurs in older adults. Although the younger age group has improved survival rate, the prognosis in older patients continues to be very poor [4].

1.1. AML Classification

French-American-British (FAB) classification and the newer World Health Organization (WHO) classification are the two of the main systems that have been used to classify AML into subtypes.

1.1.1. World Health Organization (WHO) classification

The WHO approach to disease classification endeavors to characterize the clinicopathologic entities based on a combination of clinical highlights, morphology, immunophenotype, cytogenetics, and molecular genetics. This method was first used in the third edition WHO Classification in 2001 for AML which was a major difference from the primarily morphologic and cytochemical approach used by the French-American-British Cooperative Classification. The 2016 WHO Classification of AML uses all aspects of the diagnostic approach by having entities defined chiefly by clinical history, by cytogenetic results, by molecular genetics results and by morphology and immunophenotype [5]. Even though the WHO classification may be more valuable, the FAB framework is still broadly utilized (Table 1).

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Table 1
WHO classification of AML and Related Neoplasms 2016

AML with recurrent genetic abnormalities
• AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1
• AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
• APL with t(15;17)(q24;q21);PML-RARA
• AML with t(9;11)(p21.3;q23.3); KMT2A-MLLT3
• AML with t(6;9)(p23;q34.1); DEK-NUP214
• AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
• AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); RBM15-MKL1
• Provisional entity: AML with BCR-ABL1
• AML with mutated NPM1
• AML with biallelic mutations of CEBPA
• Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, Not Otherwise Specified
• AML with minimal differentiation
• AML without maturation
• AML with maturation
• Acute myelomonocytic leukemia
• Acute monoblastic/monocytic leukemia
• Pure erythroid leukemia
• Acute megakaryoblastic leukemia
• Acute basophilic leukemia
• Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
• Transient abnormal myelopoiesis (TAM)
• Myeloid leukemia associated with Down syndrome

1.2. Cytogenetics in AML

Pretreatment karyotype is the most important prognostic predictor in adult acute myeloid leukemia (AML) [6]. In acute myeloid leukemia, the cytogenetic studies have dual significance. First, cytogenetics has significantly expanded our awareness of the basic genetic mechanisms tangled in leukemogenesis hence contributing to our understanding of the significant histopathological, immunophenotypic and clinical heterogeneity of AML. Secondly chromosome variations have been shown to constitute tumor markers of diagnostic and prognostic value [7]. The rate of abnormal karyotypes in AML has been reported to be 55%–78% in grown-ups and 77%–85% in children. Still, a considerable extent of patients with AML demonstrates no chromosome variations. Recent data demonstrate that an extent of cytogenetically normal patients show submicroscopic gene alterations that can only be recognized by molecular methods [8].

The identification of recurrent cytogenetic variations associated with different clinical presentation in AML cleared the way for the joining of genetic markers into clinical decision-making [9]. Based on the genetic origin of the disease the major recurrent cytogenetic abnormalities occur in AML are t(8;21) (q22;q22), t(15;17)(q22;q12) and inv(l6) (p13q22)/t (l6;16)(p13;q22) emerge as markers for predicting the most favorable outcome and are associated with longer remission and survival. A number of karyotypic abnormalities such as monosomies of chromosomes 5 and/or 7, deletion of the long arm of chromosome 5, and abnormalities of the long arm of chromosome 3, such as inv (3)(q21q26) and t(3;3)(q21;q26) or complex karyotype (ie, 5 or more unrelated cytogenetic abnormalities) have been correlated with a poor response to initial therapy and significantly increased risk of relapse. These are categorized as adverse prognosis group with shorter overall survival [10,11]. In contrast, about 40%–50% of all AML cases are cytogenetically normal (CN-AML) and this group has an intermediate risk of relapse [12].

1.3. Genomics of AML

For more than three decades the molecular pathogenesis of AML has been studied with the use of cytogenetic analysis. Recurrent chromosomal structural abnormalities are well recognized as diagnostic and prognostic markers, suggesting that acquired genetic abnormalities have a crucial role in pathogenesis [13]. (Fig. 1). The molecular abnormalities such as gene mutations or deregulated gene expression revealing the enormous heterogeneity among such cytogenetically defined subgroups [14]. Genetics comprising both classical cytogenetic and the mutational status of various genes is the most important predictor of prognosis (Table 2).

Scientific breakthroughs have not only improved our understanding of the molecular underpinnings of AML but also resulted in the development of several targeted therapies with greater efficacy and lesser toxicities than conventional chemotherapy. The FDA approval of small molecule inhibitors for specific AML subsets highlights the significance of genetic and molecular profiling to optimally personalize AML therapy in the modern era [15] (Table 3).

1.4. Mutations in AML

In several genes, somatically acquired mutations have been identified. Generally, these mutations are found most often in CN-AML but are related to other cytogenetic subgroups also [16,17]. The somatic mutations in AML are classified mainly into two types; they are the “driver” mutations, which provide a selective advantage, and “passenger” mutations, which were present in the original transformed cell before it started its clonal expansion [18]. Driver mutations includes Class I mutations confer a proliferative and/or survival advantage to haematopoietic progenitors, but do not have any effect on haematopoietic differentiation, Class II mutations that block haematopoietic differentiation and/or enhance self-renewal by altered transcription factors and new gene mutations, which are found in the epigenome-associated enzymes and the molecules as Class III mutations [19].

1.4.1. Mutations affecting signal transduction pathways

1.4.1.1. Fms-Like Tyrosine Kinase 3 (FLT3) mutations. The FMS-like tyrosine kinase 3 (FLT3) gene which is located on chromosome 13q12 and encodes a membrane-bound receptor tyrosine kinase (RTK) that belongs to the RTK subclass III family. It is also known as stem cell kinase 1 (STK1) or fetal liver kinase 2 (Flk2). This receptor is composed of an immunoglobulin-like extracellular ligand-binding domain, a transmembrane domain, a juxtamembrane dimerization domain, and a highly conserved intracellular kinase domain consist of protein tyrosine kinase (PTK) domains linked by a kinase-insert domain [20,21]. FLT3 is one of the most recurrent somatic mutation in AML, found in 25–45% of all AML patients [20]. Due to genetic alterations of FLT3, a constitutively activated tyrosine kinase receptor in AML blasts gets expressed and this activation leads to leukemogenesis, thus regulating the functional characteristics of leukemic blasts [22]. In AML patients, two types of activating mutations have been identified: Internal Tandem Duplication (ITD)in the region coding for the JM domain, determined by the insertion of repeated amino acid sequences, and point mutations that cause amino acid substitution in the activation loop of the Tyrosine Kinase Domain (TKD) [23].

ITD is the most common FLT3 mutation found in AML patients. The ITD mutations involve an in-frame duplication of 3−400bp in the region encoding the JM domain [24]. ITDs result in ligand-independent dimerization and tyrosine autophosphorylation of the receptor as well as activation of the RAS/MAPK, STAT5 and PI3K/AKT pathways [14]. FLT3-ITD is a major mutation that represents with a high leukemic problem, confers poor prognosis and in the management of patients with AML, ITD has a significant negative impact [25]. FLT3-ITD are more frequently associated with normal karyotype, t(15;17)/PML-RARA and t (6;9)/DEK-CAN, t(15;16) and are prognostically unfavorable in AML patients. In the elderly patients, the presence of ITD was significantly associated with worse effects on Complete Remission duration (CRD)

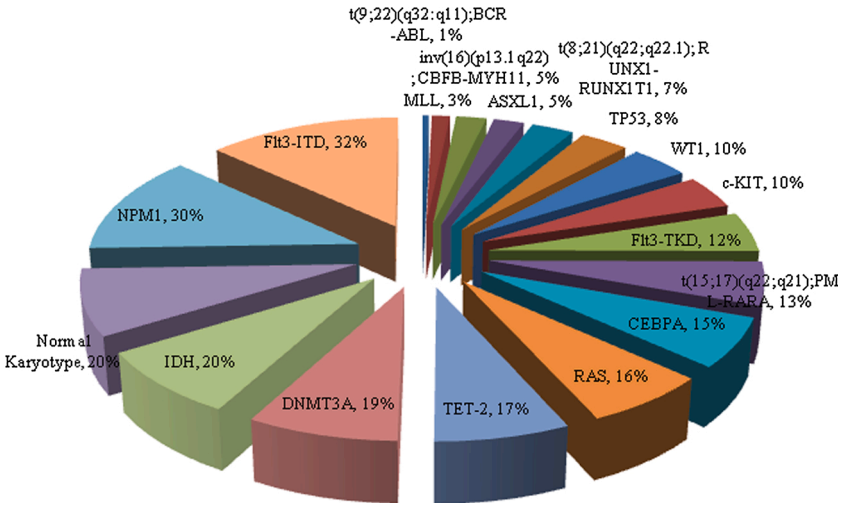

Fig. 1. Cytogenetic and molecular distribution pattern of different subsets of acute myeloid leukemia patients. AML is characterized by the presence of large number of chromosomal rearrangements which results in the generation of oncoproteins, considered to be the initiating events in disease pathogenesis. In addition to these translocations, gene mutations also make AML a heterogeneous disease. There is also a mutual exclusivity between the cytogenetic and molecular patterns, so that the AML can be classified prognostically and biologically into different subsets.

Table 2
Prognostic stratification based on Cytogenetic and Molecular alterations

RISK GROUPS	ABNORMALITIES
• FAVOURABLE	• 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-ITDlow= allelic ratio < 0.5 • Biallelic mutated CEBPA
• INTERMEDIATE	• Mutated NPM1 and FLT3-ITDhigh = allelic ratio > 0.5 • Wild-type NPM1 without FLT3-ITD or with FLT3-ITDlow (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3); MLLT3-KMT2A • Cytogenetic abnormalities not classified as favorable or adverse
• POOR	• 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-ITDhigh† • Mutated RUNX1 • Mutated ASXL1 • Mutated TP53

and Overall Survival (OS) [26]. Recently, a classification system for patients has been proposed using the FLT3-ITD allelic ratio (AR), in which nucleophosmin (NPM1) mutation coupled with a low FLT3-ITD AR indicates a favorable prognosis. Based on these more recent studies, the 2017 ELN recommendations put forward the current NPM1/FLT3-ITD risk categories that are based on an ITD AR cutoff of 0.5 and the NPM1 mutational status [27,28]. FLT3-TKD mutations are not very common while comparing with ITD [18,29]. Various studies have reported that, the clinical significance of FLT3-TKD mutations is unclear, and also it has no significant impact on Overall Survival (OS) and Event Free Survival (EFS) [30]. It can be assumed that a single study might be inadequate to accurately determine the effect of TKD mutation, because of the relatively infrequent occurrence of this mutation [31].

The FLT3 RTK, identified as frequently mutated in AML, was a natural therapeutic target for drug development. Based on their specificity for FLT3 gene, the FLT3 inhibitors are typically classified into first and second generations. First generation inhibitors are typically multikinase inhibitors. While second generation inhibitors are more specific for FLT3 gene, and usually have less off target effects such as myelosuppression, gastrointestinal toxicity, and palmo-plantar erythrodysesthesia [32]. The first-generation FLT3 inhibitors, including tandutinib, sunitinib, midostaurin, lestaurtinib and sorafenib, but because of low clinical efficacy and adverse events the clinical efficacy as a monotherapy of the first-generation FLT3 inhibitors for AML was unimpressive in early phase studies. Therefore midostaurin, lestaurtinib and sorafenib were

Table 3
Overview of New agents for AML with recent U.S. FDA approval

Mutations	Frequency in AML	Prognosis	Drugs	US FDA Approval	Drug Target
Flt3 ITD	27 - 34%	Unfavourable	Midostaurin, Quizartinib, Gilteritinib	April 2017 None (Phase II – III clinical trials) November 2018	Tyrosine kinase
Flt3 TKD	11 - 12%	Unknown			
c-KIT	10 - 25%	Unfavourable	Imatinib, Dasatinib	None (Phase II clinical trial) None (Phase III trial)	Kinase
RAS	NRAS 11 - 30% KRAS 15%	Neutral	Tipifarnib		Farnesyl transferase
NPM1	30 - 50%	Favourable	Gemtuzumab-ozogamicin	September 1, 2017	CD - 33
CEBPA	15 - 19%	Favourable			
RUNX1	5 - 15%	Unfavourable			
DNMT3A	18 - 22%	Unfavourable			
IDH1/IDH2	IDH1 7 - 14% IDH2 8 - 19%	Controversial	Ivosidenib Enasidenib	July 2018 August 2017	IDH1 & IDH2 protein
TET2	7.7 - 27.4%	Unfavourable			
ASXL1	5%	Unfavourable			
WT1	10%	Unfavourable			
TP53	5 - 20%	Unfavourable			

evaluated in combination with chemotherapies for AML with FLT3 mutations. The addition of lestaurtinib or sorafenib to conventional chemotherapy did not show benefits in clinical trials,but a randomized phase 3 study (RATIFY study) demonstrated the superiority of midostaurin in addition to the conventional induction and consolidation chemotherapies for overall survival (OS) [33].

The second-generation FLT3 inhibitors are developed to selectively inhibit FLT3 and include quizartinib, gilteritinib, and crenolanib. Patients treated with gilteritinib had a significantly longer median overall survival than the chemotherapy group. However those who received gilteritinib there were no significant difference in the median overall survival between FLT3-ITD and FLT3-TKD mutant [34]. Crenolanib, a potent type I FLT3 specific inhibitor, was investigated in a phase II trial in combination with 7 + 3 induction therapy in 29 patients with FLT-3 mutation and CR was achieved in 72% (21/29) after one cycle of induction [35]. The efficacy of sorafenib in treating relapsed *FLT3-ITD* patients has been long been established and a study including a cohort of 29 relapsed *FLT3-ITD* AML patients treated with sorafenib monotherapy showed better complete remission(CR) and appears to be effective and associated with long-term disease control in a subset of patients relapsing after allo-SCT. Quizartinib was evaluated in relapsed/refractory AML patients irrespective of *FLT3-ITD* mutation status in a phase I, first-in-human study, all while maintaining an acceptable toxicity profile. Gilteritinib has favorable safety profile along with its ability to induce response in half of relapsed/refractory AML patients due to its potent *FLT3* inhibition [36].

1.4.1.2. c-KIT mutations. The KIT gene is located at chromosome band 4q11−12,14. It encodes a 145-kD transmembrane glycoprotein, which is a member of the type III receptor tyrosine kinase family [37]. About 60–80% AML patients shows high expression of C-KIT and in 33.3–45% of AML with inv (16) and 12.8–46.8% of AML M2 with t (8;21) point mutations of C-KIT have been identified [32]. Two types of mutations occur in KIT gene; loss of function mutation and gain of function mutation. Gain of function mutation is of two types;Val560Gly and Asp816Val in the Juxtamembrane domain and in the second part of the kinase domain of Kit, respectively [38]. In CBF AML and in other human malignancies (GI stromal tumors, mastocytosis and germ cell tumors) through gain-of-function mutations, ligand-independent activation of KIT can be occurred. There is no equal distribution of c-KIT mutations among FAB subtypes and are mainly found in M1, M4, M4eo and particularly in M2. Meanwhile nearly 70% of c-KIT-mutated AML patients are classified as M2 [18]. In AML patients with t (8;21), the presence of c-KIT mutation are allied with a significantly higher incidence of relapse and a poor survival [39] but not in patients with normal karyotype [40]. But the prognostic impact of KIT mutations in AML with inv (16) remains controversial [39].

In contrast to the recent knowledge with FLT3, no other activated kinase has yet clearly confirmed to be an effective therapeutic target in AML. No clinical trials have assessed the effectiveness of KIT inhibitors in AML patients with *KIT* mutations; remarkably, all clinically available KIT inhibitors appear to be inactive against KIT D816 mutations [41,36]. Many TKIs such SU5416, SU6668, Gleevec or imatinib have some activity against KIT. Imatinib prevent autophosphorylation of c-KIT and also the activation of the downstream signal transducers MAPK and Akt [42], SU5416 is a multi-RTK inhibitor also effective against c-kit. But in patients with refractory AML, only a partial response was observed. Dasatinib (BMS-354,825) is another potent dual Src/Abl tyrosine kinase inhibitor with clinical efficacy against IM-resistant c-KIT mutants and patients with refractory AML [43]. Other RTK inhibitors, such as sunitinib, nilotinib, PKC412, EXEL-0862, and OSI-930, showed activity against a variety of c-KIT mutations [44].

1.4.1.3. Ras mutations. The RAS oncogene family was the first specific human oncogene discovered in human cancer. It has been broadly studied over the last 3 decades. RAS gene is named for “rat sarcoma.” [45] The Ras proto-oncogene belongs to the small GTPase family. It exists in 3 distinct isoforms, N-Ras, K-Ras, and H-Ras [46]. In AML, the frequency of occurrence of RAS mutations is about 15–40% [47]. NRAS mutations seem to be the most prominent RAS mutations in patients with AML than those with K-Ras, and H-Ras mutations. NRAS mutations have been reported in 11%–30% of patients [48]. In AML, the prognostic effect of NRAS mutations is still under discussion [47,48]. There is a predominance of N-ras mutation in M4 subtype occurring at a rate of about 60%–80% among patients [49]. K-Ras mutation also found in M4 subtypes with a 20% frequency [50]. Farnesyltransferase inhibitors (FTIs) are the major class of directed RAS-targeted therapeutics that has been investigated. In AML a single phase 2 trial did demonstrate activity with FTI therapy (tipifarnib) with occasional complete responses. Off-target side effects were observed in these trials [51].

1.4.2. Mutation in nucleophosmin

1.4.2.1. Nucleophosmin 1 (NPM1) mutations. Nucleophosmin (NPM1), also known as B23, No38 or Numatrin, is an abundant nucleolar protein mainly found in the nuclei of proliferating cells [52]. Ribosome biogenesis, DNA repair and regulation of apoptosis etc. are the major cellular functions performed by NPM1. NPM1 mutations emerge as a distinct AML entity even though it is a rather late event in leukemogenesis [53]. Though the bulk of NPM1 be located in the granular region of the nucleolus, it shuttles continuously between nucleus and cytoplasm. So mutation in exon 12 of the NPM1 gene on chromosome 5q35 leads to a frameshift and an elongated protein results in aberrant localization of the protein to the cytosol [54,55]. NPM1 mutations have been found in approximately 30% of adults with de novo AML. The incidence of NPM1 mutation significantly higher in older compared to younger adults and it has been found to occur in an age-dependent fashion [56], NPM1 mutations were found in patients with AML of all FAB subtypes except M3 [56,57]. NPM1 mutations occur predominantly in CN-AML i.e. about 50% of CN-AML are NPM1 mutated [57]. In patients with AML and normal karyotype, NPM1 mutations alone were found to have a considerably improved Overall Survival (OS) and Disease Free Survival (DFS) as well as a lower incidence of relapse [55]. In leukemogenesis, NPM1 mutations cooperate with other gene mutations. It is also found that approximately 40% of patients with NPM1 mutations also carry FLT3 internal tandem duplications (FLT3-ITD), and several studies solidly indicated that the genotype mutant NPM1 without FLT3-ITD represents a favorable prognostic marker in patients. NPM1 mutations along with DNMT3A are known to favorably affect prognosis of AML patients [58]. In addition to these genes, NPM1 mutations are also associated with C/EBPα (13%), MLL-PTD (7%) and NRAS (13%) mutations.

Adult fit AML patients (≤ 60 years) with NPM1-mutatation are treated with intensive chemotherapy. The expression levels of CD33 in NPM1- mutated AML are high, that is druggable with gemtuzumab ozogamicin. Adding this agent to chemotherapy improved event-free survival and OS in one study, but resulted in lower relapse incidence with no survival advantage in another [59]. Now a days, NPM1-mutated AML patients with FLT3-ITD high (ratio ≥0.5) should receive conventional chemotherapy plus a FLT3 inhibitor [60]. Older fit patients (>60 years) with NPM1-mutated AML treated with intensive chemotherapy experience 15–20% long-term survival and these results may be ameliorated using venetoclax, an oral BCL-2 inhibitor, combined with hypomethylating agents(HMA). In unfit older adult with NPM1 mutation, hypomethylating agent (HMA) therapy represents a feasible alternative to intensive chemotherapy(IC), although outcomes with HMA monotherapy remain poor (overall response rate, 45.5%; CR, 23.5%; median OS, ~10 months). The recent approval of venetoclax (VEN; 400 mg daily), in combination with HMAs in older, chemotherapy-unfit NPM1 mutated AML patients has demonstrated

remarkable effectiveness in inducing CR [59,61].

1.4.3. Mutations affecting transcription factor

1.4.3.1. CCAAT Enhancer Binding Protein α (CEBPA) mutations. The CCAAT/enhancer-binding protein-alpha (CEBPA) gene located on chromosome 19 band q13.1.The CEBPA is a transcriptional factor that plays a vital role in regulating the proliferation and differentiation of myeloid precursors [62]. CEBPA mutations occur in 15–19% of CN-AML patients and typical in patients with French-American-British (FAB) subtype M2 [62,63]. As a result of t(8;21) (q22; q22) translocation in AML M2 subtype patients, the resulting AML1-ETO fusion protein down regulates CEBPA expression to levels which is insufficient for granulocyte differentiation [63]. There are two major types of CEBPA mutations; first is a nonsense mutation in the N-terminal region of the gene, thus preventing expression of the full-length CEBPA protein, which ultimately upregulates the formation of a truncated isoform with dominant negative properties, and the second is an in-frame mutation in the C-terminal basic region-leucine zipper domain results in a CEBPA protein with decreased DNA binding or dimerization activity. Although both occurs concurrently, either in a monoallelic or biallelic fashion and CEBPAbi is a favourable prognostic marker in AML, with increased overall survival (OS) and event-free survival (EFS) while compared to CEBPA-wild-type (CEBPAwt) or monoallelic CEBPA-mutated patients [63,64]. CEBPA mutations were mostly observed in patients from the intermediate cytogenetic risk subgroup [65] and also they do not co-occur with other recurrent fusion genes like PML-RARA, CBFB-MYH11 or RUNX1-RUNX1T1 [66]. Irrespective of the presence or absence of other prognostic predictors like FLT3, NPM1, WT1 patients with CEBPA mutations have potentially lower risk of experiencing induction treatment failure, experiencing relapse, or dying i.e., with better relapse free survival(RFS) and overall survival(OS) [67].

1.4.3.2. Runt-related transcription factor (RUNX1) mutations. The runt-related transcription factor 1 (AML1/RUNX1) gene encodes the subunit of core binding factor [68]. It is a heterodimeric transcription factor which is required for definitive hematopoiesis. The AML1/RUNX1 also known as RUNX1 gene,consisting of 10 exons and is one of the most commonly mutated genes in leukemia through chromosomal translocations and point mutations [69]. It is located at chromosome 21 and its frequent translocation with the ETO/MTG8/RUNX1T1 gene located on chromosome 8q22 results in a fusion protein AML-ETO or t(8;21) (q22;q22) AML [12]. Point mutations in RUNX1 gene were most frequently found in the AML M0 subtype and is a biallelic mutation and also associated with tisomy 13 and trisomy 21 [70,12]. In patients with cytogenetically heterogeneous AML, mutations in RUNX1 are associated with a poor prognosis including a lower complete remission rate, shorter relapse-free survival and shorter overall survival [71].

1.4.4. Mutation in epigenetic modifiers

1.4.4.1. DNA methyltransferase 3A (DNMT3A) mutations. DNMT3A encodes for the enzyme DNA (cytosine-5) - methyltransferase 3A. It belongs to the family of other methyltransferases like DNMT1 and DNMT3B.The major functions of these enzymes are that they involved in adding methyl groups to the cytosine residue of CpG dinucleotides and thus play an important role in the epigenetic regulation of genes. DNAmethyltansferase 3A (DNMT3A) gene mutation occurs in 18%–22% of all AML cases and in about 34% of CN-AML [12]. The mutation in DNMT3A involves a missense mutation affecting arginine codon 882 (R882-DNMT3A) is more common while comparing to those affecting other codons (non-R882-DNMT3A) resulting in a defect in normal hematopoiesis and proper methylation [11,72]. In a large group of AML patients, recurrent DNMT3A mutations were subsequently detected at multiple sites, including codon R882 [72]. DNMT3A mutations frequently occur in AML with a normal karyotype and associated with French-American-British (FAB) M5 morphology [72,73]. Also, DNMT3A mutations are associated with other mutation like NPM1, FLT3, and IDH1 more recurrently [73,74]. In CN-AML patients with wild-type NPM1 and wild-type FLT3, the DNMT3A mutations have a negative prognostic effect [75]. While comparing to patients with wild-type *DNMT3A*, the prognosis of patients harboring *DNMT3A* R882 mutation seems to be worse, although large prospective studies are not available yet. Until then, to determine the prognosis of these patients, other validated parameters should be considered, such as age, cytogenetic abnormalities, minimal residual disease (MRD) and presence of other mutations [76].

1.4.4.2. Isocitrate dehydrogenase (IDH) mutations. IDH1 and IDH2 genes code for NADP-dependent isocitrate dehydrogenase located in the cytosol and mitochondria, respectively. These enzymes catalyze decarboxylation of isocitrate into alpha-ketoglutarate in the tricarboxylic acid cycle; this alpha-ketoglutarate is used by TET proteins during histone demethylation [77]. IDH1 and IDH2 genes located on chromosome 2q33 and 16q26, respectively. In AML, IDH2 gene is most frequently mutated, affecting 8–19% patients, with an increasing incidence in intermediate risk and older patient populations [78]. *IDH1* mutation occurs in 7−14% of AML patients, that typically involves a cysteine (R132C) or histidine (R132 H) substitution for arginine at R132. While IDH2-R140 mutations are more common than *IDH2*-R172 mutations [78,79]. IDH2 mutation is an independent favorable prognostic factor in all non-M3 or cytogenetically normal AML but IDH1 mutations were associated with worse overall survival and event-free survival especially in patients with normal cytogenetics [78,80]. In two large studies, patients with either IDH1/IDH2 mutations were significantly enriched with NPM1 mutations. Among the entire cohort of patients it has found that those with an IDH2-R140Q mutation had an improved overall survival and decreased response rate [81]. IDH1/2 mutations in conjunction with NPM1-mutant and FLT3-ITD negative molecular status have been associated mostly with favorable outcome in otherwise intermediate-risk AML. While other large studies have identified that patients with IDH mutations including the NPM1-mutated IDH-mutated with worse overall survival, and other studies report a lack of prognostic significance [82]. The impact of *IDH* mutations on AML prognosis remains somewhat controversial, even though a generally poorer outcome is seen with *IDH1* mutations and a relatively favorable prognosis may be seen with *IDH2* mutations, particularly R172 K IDH2 mutations, in the setting of standard intensive chemotherapy [83].

Ivosidenib and enasidenib are the two targeted IDH1 drugs, work by blocking the proteins IDH1 and IDH2, respectively. This inhibition allows the normal maturation and differentiation of leukemic white blood cells, thereby reducing immature blast counts and increasing the percentage of mature myoblasts [84]. A dose finding study mainly in relapsed/refractory-AML patients with the selective and potent IDH2 inhibitor enasidenib (AG-221) showed it as a single promising agent in patients with mutated IDH2. Overall, 40% (71/176) relapsed/refractory-AML patients irrespective of the mutation types IDH2-R140 or IDH2-R172 achieved a response and 66 of them had <5% bone marrow blasts. Similar results have been reported from a phase I trial with AG-120 (ivosidenib) another IDH1 inhibitor [85]. Further studies are ongoing by combining enasidenib with azacitidine in relapse (identifier: NCT03683433) or ivosidenib with azacitidine in upfront AML patients(identifier: NCT03173248). Preliminary results of a phase II study in which these inhibitors were tested in combination with standard induction chemotherapy in upfront patients with the appropriate mutation showed a response rate of 93% in the ivosidenib wing and 73% in the enasidenib wing, with mutational clearance of 41% and 30% respectively [86]. Two randomized phase III studies, one for patients eligible for intensive treatment, the HOVON/AML-SG AML study (NCT03839771) in which ivosidenib is added to intensive

chemotherapy, consolidation and maintenance, and one for patients ineligible for non-intensive treatment in which ivosidenib is combined with azacitidine, the AGILE study (NCT03173248) are currently ongoing [87].

1.4.4.3. Ten–eleven translocation 2 (TET2) mutations. TET (Ten-Eleven translocation) proteins function through conversion of 5-methylcytosines (5mC) to 5-hydroxymethylcytosine (5hmC) thus play an important role in DNA demethylation and results in an epigenetic regulation [12,21,88]. The TET oncogene family member 2 (TET2) gene was identified to be mutated in a variety of myeloid disorders [89]. Through epigenetic modification, mutant TET2 dysregulate the function of hematopoietic stem cell [90]. TET2 mutations involves deletions, nonsense mutations, and missense mutations at highly conserved residues. These mutations are supposed to inactivate the function of the enzyme and this results in clonal expansion of HSCs in humans and is an early event in AML leukemogenesis [91]. TET2 mutations can associate with other gene mutations, including NPM1, FLT3, JAK2, RUNX1, CEBPA, CBL and KRAS, but they are almost mutually exclusive with IDH1/2 mutations [92]. About 7.7–27.4% of patients with AML have been reported with TET2 mutations [88,92]. Despite several studies, the overall prognostic significance of TET2 mutation remains unclear. Abdel-Wahab et al. 2009 reported that while compared with TET2-wild-type AML patients TET2 mutations are associated with decreased overall survival in AML [93]. But according to Nibourel et al. 2010; there was no difference in Disease Free Survival (DFS) or OS between patients with and without TET2 alteration in patients with AML who achieved CR [94].

1.4.4.4. Additional sex comb-like 1 (ASXL1) mutations. The additional sex combs like-1 (ASXL1) gene, located in chromosome band 20q11, encodes a highly conserved protein that belongs to the enhancer of trithorax and polycomb (ETP) gene family [95]. In de novo AML, the occurrence of ASXL1 mutations is about 5%, whereas some studies suggest a higher prevalence (30%) in secondary AML. ASXL1 mutations occurred more frequently in older (>60) and male patients (10), also closely associated with FAB M0 subtype. ASXL1 mutations were highly correlated with trisomy 8, RUNX1 mutation, but there is an inverse association with t(15;17), complex cytogenetics, FLT3-ITD, NPM1 mutations, WT1 mutations [96].

1.4.5. Mutation in tumor suppressor genes

1.4.5.1. Wilm's tumor 1(WT1) mutations. The WT1 gene is located at chromosome 11p13 [97]. It encodes a protein with four C-terminal Zn-fingers which is the characteristics of transcription factors and the N-terminal region, in conjunction with the DNA-binding domain, can autonomously repress or activate transcription [98]. It is observed that the WT1 gene is overexpressed in various leukemias, particularly AML and also in the case of other cancers and hence it is recommended to be an oncogene. On the other hand, approximately 10% of AML patients are found with WT1 gene mutation with hotspots in the 4 Cys-His zinc finger domains on exons 7 and 9 [99]. In approximately 10% of CN-AML, WT1 mutations occur and it cluster to exons 7 and 9 and that these mutations alone forecast poor prognosis in patients with CN-AML [100]. As a poor prognostic indicator, WT1 mutations were most strongly associated with induction failure, and exerting an impact thereafter on Cumulative Incidence of Relapse(CIR), Relapse Free Survival(RFS), and OS [101]. The presence of FLT3-ITD along with WT1 mutation may result in induction failure and worse outcome [102].

1.4.5.2. Tumor protein 53 (TP53) mutations. The TP53 is a tumor suppressor gene that encodes for the transcription factor p53 and is the most frequently mutated gene in human cancer [103]. It contols cell cycle arrest, apoptosis, senescence and DNA repair. Initially it has been described as "the guardian of the genome" referring to its role in preserving genome stability through the prevention of mutations [104]. In AML, TP53 mutations are associated with older age, lower blast counts (both in the bone marrow and in the peripheral blood), adverse risk karyotypes, and exposure to previous chemotherapy. Generally, TP53 mutations may occur in almost all FAB morphologic subtypes, although there is a modest enhancement in M6-erythroleukemias (25%–36%) [105]. Several independent reports suggested that aberrations of TP53 are associated with an exceedingly adverse prognosis. Compared with de novo disease, therapy related-AML/therapy related-MDS (t-AML/t-MDS) have a higher frequency of TP53 mutations, also TP53 mutated t-AML is associated with complex karyotype and higher risk cytogenetics. Various studies have shown that TP53 mutated AML is associated with poor outcomes to conventional induction chemotherapy [106]. In complex-karyotype AML, the TP53 mutation rate is ~70% and also TP53 mutations are the most common molecular lesion [107]. In AML, TP53 mutations are mutual exclusive with other mutated genes such as NPM1, FLT3, MDM2, and ARF [108].

APR-246 is a novel small molecule that targets and reactivates mutant TP53 leading to cell death through the restoration of the wild-type form of TP53 and has previously demonstrated single-agent activity in AML [106]. HSP90 inhibitors have been shown to increase degradation of mutant *TP53,* yet, clinical trials in myeloid diseases have not produced favorable results. Statins, widely used to lower the blood cholesterol level, have been shown to induce degradation of abnormal p53 protein, inhibit tumor growth in *TP53* mutated tumor cells and work synergistically with chemotherapeutic agents, representing a possible novel agent that could be added to conventional and investigational therapies [109].

1.5. Gene expressions in AML

Similar to gene mutations, increasing the transcript dose of certain genes results in mere overexpression that in turn initiate leukemogenic event to confer a proliferation and or self-renewal advantage to leukemic cells [110]. Overexpressions of a number of genes, such as BAALC, ERG, MN1 or EVI1 are shown to be prognostically significant. The mechanisms by which these genes become deregulated remain obscure. Translocations, inversions or gene amplifications are found these genes, but in general overexpression occurs in the absence of such rearrangements. But in these genes no activating mutations have so far been identified [111]. Gene-expression profiling allows a comprehensive classification of AML that includes previously identified genetically defined subgroups that have been shown to be of prognostic significance [112].

1.5.1. Brain and acute leukemia, cytoplasmic (BAALC) gene

The BAALC gene, located in chromosome band 8q22Æ3. It encodes a protein that has no homology to known proteins or functional domains. The expression of BAALC gene was mostly identified in hematopoietic precursors and neuroectoderm-derived tissues [113]. High expression of BAALC gene was earlier established as an independent poor prognostic factor in CN-AML [114]. After intensive chemotherapy and autologous transplantation, only 39% of patients with high BAALC expression were alive for 3 years and only 39% of those achieving CR remained in continuous CR. While in the case of low BAALC expressers 60% were alive and 68% of those achieving CR remained continuously disease-free at 3 years [115,107]. In $FLT3^{ITD/WT}$ and $FLT3^{WT/WT}$ patients, high BAALC expression remained a significant adverse prognostic factor when compared to those with low BAALC expression [113].

1.5.2. Meningioma 1 (MN1)

MN1 is an oncogene found on the long arm of human chromosome 22. Through its function as transcription co-regulator MN1 protein has an important role in normal proliferation of hematological and other body cells. It has been identified as a contributing factor to both hematological and solid malignancies [116]. In CN-AML patients, the over

expression of *MN1* predicted worse outcome [117]. One of the most important finding related to MN1 overexpression is that, it is associated with treatment failure, specifically a significantly worse day 15 response rate, higher relapse rate, and shorter relapse-free and overall survivals. The mechanism that leads to the treatment failure or leukemogenesis through the overexpression of MN1 remains unknown [118]. MN1 is the target of balanced t(12;22) and also overexpressed in inv(16)(p13;q22) [119].

1.5.3. The ETS-related gene (ERG)

ETS-related gene (ERG) is located at chromosome band 21q22. ERG is a member of the ETS family of transcription factors. ERG and other members of the family are downstream effectors of mitogenic signaling transduction pathways and are involved in key steps regulating cell proliferation, differentiation, and apoptosis [120]. ERG plays an important role in fetal hematopoiesis and hematopoietic stem cell (HSC) maintenance [121]. ERG gene is a molecular marker predicting adverse outcome of CN-AML patients. In patients with complex karyotypes and abnormal chromosome 21, the overexpression of the ERG gene was first discovered [115,122]. CN-AML patients with high ERG expression were less likely to respond to induction chemotherapy with a lower CR rate, but their early death rate (within 28 days) was similar to patients with low ERG expression. Patients with FLT3 ITD and high ERG levels have poor prognostic effect. Thus high ERG levels primarily seem to predict resistance to induction chemotherapy and early treatment failure [123].

2. Conclusion

AML is a complex and heterogeneous disease. Pretreatment karyotype is one of the important criteria for risk stratification of AML, based on which the response to therapy and survival can be predicted. But now a day, the identification of new molecular biomarkers aids in refining the cytogenetically classified patient subclasses. In recent years, few markers enter into clinical practices, for example; FLT3 inhibitors are a momentous drug discovery in AML treatment. Still, new panels of molecular markers are increasing in AML. These findings help to understand novel drug targets. So the development of new treatment in connection with accurate risk stratification and genetic profiling is expected to improve the survival of patients. Now we are looking forward for a time during which AML will be treated with novel drugs that provides better overall survival for patients with relapsed disease and for those who are in poor cytogenetic subsets.

Declaration of Competing Interest

None.

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