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Chapter

Current Cytogenetic Abnormalities in Acute Myeloid Leukemia

Mounia Bendari, Nisrine Khoubila, Siham Cherkaoui, Nezha Hda, Meryem Qachouh, Mouna Lamchahab and Asmaa Quessar

Abstract

Cytogenetic abnormalities are frequently reported in the literature describing the presence of chromosomal rearrangements in important cases of acute myeloid leukemia (AML); the rate can reach 50–60% of cases of AML. Cytogenetic abnormalities represent an important prognosis factor, their analysis is crucial for AML; cytogenetic study permits to classify prognostic groups and indicate the treatment strategy and helps to improve the outcome of these patients and to increase their chances of cure. Hundreds of uncommon chromosomal aberrations from AML exist. This chapter summarizes chromosomal abnormalities that are common and classifies AML according to the World Health Organization (WHO) classifications from 2008 to 2016; we will discuss briefly gene mutations detected in normal karyotype (NK) AML by cutting-edge next-generation sequencing technology, like FLT3-ITD, nucleophosmin (NPM1), CCAAT/enhancer-binding protein alpha (CEBPA), and other additional mutations.

Keywords: cytogenetic abnormalities, acute myeloid leukemia, karyotype

1. Introduction

Acute myeloid leukemia (AML) is characterized by clonal expansion of undifferentiated myeloid precursors, resulting in impaired hematopoiesis and bone marrow failure [1].

The discovery of specific chromosomal abnormalities has proved that leukemia is a genetic disease on the cellular level and has also guided the way to mapping and cloning of genes involved in the leukemic process.

The frequency of cytogenetic abnormalities is reported in the literature describing the presence of chromosomal rearrangements in important cases of AML; they are recognized in approximately 56% of de novo AML in adults [2, 3], and the rate can reach 70–80% of the cases of AML in children [4, 5]. At present, cytogenetic aberrations detected at the time of AML diagnosis constitute the most common basis for predicting clinical outcome [6].

Karyotype analysis must be performed as part of the standard diagnostic procedure of AML and have to be reported according to the International System for Nomenclature in Human Cytogenetic (ISCN) 3.

AML appears as a complex and evaluative disease [7, 8]. There are many leukemia genes, most of which are infrequently mutated, and patients typically have more than one driver mutation. The AML evolved over time, with multiple competing clones coexisting at any time [7, 8].

The analysis of cytogenetic abnormalities is indispensable for AML; it represents the most important prognosis factor for patients with AML. In fact, cytogenetic study helps to classify prognosis groups and guide the treatment strategy and permits to improve the outcome of these patients and to increase their chances of cure.

Many uncommon chromosomal aberrations from AML exist. This chapter resumes chromosomal abnormalities that are common in structural and numerical aberrations. Cytogenetic and mutational data are used to divide patients into subgroups defined according to prognostic factors and factors that dictate whether allogeneic hematopoietic stem cell transplantation should be performed during an initial remission.

2. Recurrent cytogenetic abnormalities

2.1 The t(8;21) (q22;q22.1); *RUNX1-RUNX1T1*

The t(8;21) (q22;q22.1); *RUNX1-RUNX1T1* abnormality is considered as a subset with particular clinical and biological specificities. This translocation is defined by fusion between the AML1 gene (RUNX1) on chromosome 21 and the ETO gene (this translocation can be referred to as the RUNX1T1 gene that encodes the CBFA2T1 protein) on chromosome 8. The t(8;21) abnormality is found in approximately 5–10% of all AML cases and 10–22% of AML cases with maturation corresponding to the previous FAB class M2. The t(8;21) generates two fusion genes, AML1-ETO and ETO-AML1, but only the AML1-ETO transcript transcribed from the derivative chromosome 8 is detectable by reverse transcriptase polymerase chain reaction (RT-PCR). Patients with t(8,21) are included in the favorable group; the prognosis after intensive chemotherapy is better for these patients than for the majority of AML patients. The incidence of t(8;21) decreases with age; it is most common in children/younger patients and uncommon in patients above 60 years of age. Approximately 10–20% of children with AML have this translocation [9].

2.2 The inv(16) (p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*

Approximately 5–7% of acute myeloid leukemia patients have an inv(16) (p13;q22) or t(16;16)(p13;q22). Molecularly, inv(16)/t(16;16) is the result of the juxtaposition of the myosin, heavy chain 11, smooth muscle gene (MYH11) at 16p13 and the core-binding factor, β subunit gene (CBFB) at 16q22; this juxtaposition creates the CBFB-MYH11 fusion gene. The genomic breakpoints can be variable within CBFB and MYH11; this variability explains why in the literature many differently sized CBFB-MYH11 fusion transcript variants have been reported. Type A is the more frequent type of fusion reported; it represents more than 85% of fusions, and 5–10% of each are type D and type E fusions. This cytogenetic group is characterized by its usually association with high complete remission (CR) rates and a relatively favorable outcome [10].

2.3 Acute promyelocytic leukemia with *PML-RARA*

The of reciprocal translocations (15;17) are usually present on acute promyelocytic leukemia (APL); this translocation involves the *PML* gene on 15q24 and *RARA*

gene on 17q21 in more than 90% of cases. *PML-RARA* fusion gene results on the derivative chromosome 15.

PML-RARA fusion can also be a result of cases of complex translocations involving 15, 17, and other partner chromosomes or insertions of 15 into 17 and vice versa. Rare variant translocations involving *RARA* and other partner genes have been reported like *PLZF*, *NPM*, *NuMA*, *STAT5b*, *PRKAR1A*, *FIP1L1*, and *BCOR* [11].

2.4 The t(9;11) (p22;q23)

Acute myeloid leukemia with t(9;11) occurs in 3–5% of cases of AML. The translocation t(9;11) (p22;q23) [subsequently referred to as t(9;11)] in acute myeloid leukemia resulting in the MLL-MLLT3-fusion protein represents the most common translocation involving *MLL.* MLL gene at 11q23 (HRX) encodes a DNA-binding protein that positively regulates expression of target genes, including multiple HOX genes, by methylation of histone H3 lys4/chromatin remodeling [12].

2.5 The t(6;9) (p23;q34)

The translocation t(6;9) is a rare recurring cytogenetic aberration and occurs in 0.7–1.8% of cases of AML. This translocation is the result of the formation of a chimeric fusion gene, DEK-NUP214 (previously known as DEK-CAN). It is associated with a poor prognosis; the remission is achieved in less than 50% of cases after chemotherapy [13].

2.6 The inv(3) (q21q26.2) or t(3;3)(q21;q26.2)

The inv(3) (q21q26.2) or t(3;3)(q21;q26.2) occurring at the long arm of chromosome 3 involves the oncogene EVI1 at 3q26.2 (or its longer form MDS1-EVI1) and RPN1 at 3q21, leading to the RPN1-EVI1 fusion transcript. These abnormalities are considered as a separate entity, characterized by an aggressive clinical behavior. RPN1 can amplify EVI1 expression resulting in increased cell proliferation and may impair cell differentiation and be responsible of hematopoietic cell transformation [14].

2.7 The t(1;22) (p13;q13)

Acute megakaryoblastic leukemia (AMKL) with t(1;22) (p13;q13) is an extremely rare subtype of acute myeloid leukemia that is almost always described in infants. The nonrandom association between t(1;22) (p13;q13) and infant AMKL was reported by Baruchel et al. [15]. Just after that, the fusion gene OTT-MAL was identified in patients with t(1;22).

3. WHO classification for myeloid neoplasm regroups

The World Health Organization (WHO) new classification for myeloid neoplasm regroups clinical cytogenetic and molecular criteria, which were associated with the morphological and immunophenotypic characteristics used in the classification recommended by the French-American-British (FAB) cooperative group [16]. The current update of the WHO classification provides few changes to the existing disease categories. The remaining subcategory AML, not otherwise specified (NOS), pure erythroid leukemia, requires more than 80% immature erythroid precursors with more than 30% proerythroblasts. The most important modification

concerned a new category "myeloid neoplasms with germ line predisposition" which has been added.

Table 1 summarizes the update of WHO classification of 2016, and **Table 2** gives more details about the new category "myeloid neoplasms with germ line predisposition" [17].

3.1 AML with recurrent genetic abnormalities

The revisit interested in the molecular basis of the LMA with inv(3) (q21.3; q26.2) or t (3; 3) (q21.3; q26.2) has demonstrated that the repositioning of a GATA2 enhancer element which is the cause of overexpression of the MECOM gene (EVI1) and haploinsufficiency of GATA2 [18, 19].

The revisit added another provisional entity; it is about "AML with BCR-ABL1." Treatment with a tyrosine kinase inhibitor for patients with this abnormality is essential. In some cases, distinguishing from blast phase of chronic myeloid leukemia can be difficult; preliminary data suggest that deletion of antigen receptor genes (immunoglobulin heavy chain and T-cell receptor), IKZF1, and/or CDKN2A would be in favor of the diagnosis of AML rather than chronic myeloid leukemia blast phase [20].

When AML is associated with mutated nucleophosmin (NPM1) or biallelic mutations of CCAAT/enhancer-binding protein alpha (CEBPA), it is recognized as full entities. AML associated with biallelic mutations of CEBPA is the only reported as purveyor for the favorable prognosis [21, 22].

Finally, a new provisional entity "AML with mutated RUNX1" (excluding cases with changes associated with myelodysplasia) has been introduced. It has been associated with distinct clinico-pharmacological features and a poor prognosis [23, 24].

3.2 AML with myelodysplasia-related changes

Many criteria were introduced for this category, like the presence of multilineage dysplasia, preexisting myeloid disorder, and/or myelodysplasia-related cytogenetic changes. The deletion 9q was also removed from the list of myelodysplasia-related cytogenetic changes, this modification was done because del9q is usually associated with t(8;21), and it also frequently occurs in AML with NPM1 and biallelic CEBPA mutations [25, 26].

3.3 AML, not otherwise specified

The subgroup with acute erythroid leukemia and erythroid/myeloid type was defined, in the past, by the presence of more than 50% bone marrow erythroid precursors and more than 20% myeloblasts among nonerythroid cells; actually myeloblasts are always counted as percentage of total marrow cells. The remaining subcategory AML, not otherwise specified, pure erythroid leukemia, is defined by the presence of 80% immature erythroid precursors with more than 30% proerythroblasts. On AML NOS, FAB classification does not give any prognosis information if NMP1 and CEBPA documentation are done [27].

3.4 Myeloid neoplasms with germ line predisposition (synonyms: familial myeloid neoplasms; familial myelodysplastic syndromes/acute leukemias)

This new category was recently included; this category needs special investigations from physicians. He must reconstitute the patient and family history.

Myeloid neoplasms with germ line predisposition (see Table 2)	
AML and related neoplasms	**AML and related neoplasms (cont'd)**
AML with recurrent genetic abnormalities	Acute myelomonocytic leukemia
AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*	Acute monoblastic/monocytic leukemia
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	Pure erythroid leukemia[#]
Acute promyelocytic leukemia with *PML-RARA*[*]	Acute megakaryoblastic leukemia
AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[†]	Acute basophilic leukemia
AML with t(6;9)(p23;q34.1); *DEK-NUP214*	Acute panmyelosis with myelofibrosis
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*	Myeloid sarcoma
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1*[‡]	Myeloid proliferations related to Down syndrome
Provisional entity: AML with *BCR-ABL1*	Transient abnormal myelopoiesis
AML with mutated *NPM1*[§]	Myeloid leukemia associated with Down syndrome
AML with biallelic mutations of *CEBPA*[§]	Blastic plasmacytoid dendritic cell neoplasm
Provisional entity: AML with mutated *RUNX1*	**Acute leukemias of ambiguous lineage**
AML with myelodysplasia-related changes[‖]	Acute undifferentiated leukemia
Therapy-related myeloid neoplasms[¶]	MPAL with t(9;22)(q34.1;q11.2); *BCR-ABL1*[**]
AML, NOS	MPAL with t(v;11q23.3); *KMT2A* rearranged
AML with minimal differentiation	MPAL, B/myeloid, NOS
AML without maturation	MPAL, T/myeloid, NOS
AML with maturation	

For a diagnosis of AML, a marrow blast count of ≥20% is required, except for AML with the recurrent genetic abnormalities t(15;17), t(8;21), inv(16), or t(16;16).
MPAL, mixed phenotype acute leukemia; NK, natural killer.
[*]*Other recurring translocations involving RARA should be reported accordingly: for example, AML with t(11;17)(q23;q12); ZBTB16-RARA; AML with t(11;17)(q13;q12); NUMA1-RARA; AML with t(5;17)(q35;q12); NPM1-RARA; or AML with STAT5B-RARA (the latter having a normal chromosome 17 on conventional cytogenetic analysis).*
[†]*Other translocations involving KMT2A (MLL) should be reported accordingly: for example, AML with t(6;11)(q27;q23.3); MLLT4-KMT2A; AML with t(11;19)(q23.3;p13.3); KMT2A-MLLT1; AML with t(11;19)(q23.3;p13.1); KMT2A-ELL; and AML with t(10;11)(p12;q23.3); MLLT10-KMT2A.*
[‡]*Rare leukemia most commonly occurring in infants.*
[§]*Diagnosis is made irrespective of the presence or absence of multilineage dysplasia.*
[‖]*At least 20% (≥20%) blood or marrow blasts and any of the following: previous history of MDS or MDS/MPN; myelodysplasia-related cytogenetic abnormality (see list below); multilineage dysplasia; and the absence of both prior cytotoxic therapy for unrelated disease and aforementioned recurring genetic abnormalities. Cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes are complex karyotype (defined as three or more chromosomal abnormalities in the absence of one of the WHO-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); unbalanced abnormalities: −7 or del(7q); −5 or del(5q); i(17q) or t(17p); −13 or del(13q); del(11q); del(12p) or t(12p); idic(X)(q13); and balanced abnormalities: t(11;16)(q23.3;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3;q21.2); t(2;11)(p21;q23.3); t(5;12)(q32;p13.2); t(5;7)(q32;q11.2); t(5;17)(q32;p13.2); t(5;10)(q32;q21.2); t(3;5)(q25.3;q35.1).*
[¶]*Cases should be classified with the related genetic abnormality given in the diagnosis.*
[#]*The former subgroup of acute erythroid leukemia and erythroid/myeloid type (≥50% bone marrow erythroid precursors and ≥ 20% myeloblasts among nonerythroid cells) was removed; myeloblasts are now always counted as percentage of total marrow cells. The remaining subcategory AML, NOS, pure erythroid leukemia, requires the presence of >80% immature erythroid precursors with ≥30% proerythroblasts.*
[**]*BCR-ABL1+ leukemia may present as MPAL; treatment should include a tyrosine kinase inhibitor.*

Table 1.
Myeloid neoplasms with germ line predisposition, AML and related precursor neoplasms, and acute leukemias of ambiguous lineage (WHO 2016).

WHO classification
Classification[*]
Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction
AML with germ line *CEBPA* mutation
Myeloid neoplasms with germ line *DDX41* mutation[†]
Myeloid neoplasms with germ line predisposition and preexisting platelet disorders
Myeloid neoplasms with germ line *RUNX1* mutation[†]
Myeloid neoplasms with germ line *ANKRD26* mutation[†]
Myeloid neoplasms with germ line *ETV6* mutation[†]
Myeloid neoplasms with germ line predisposition and other organ dysfunction
Myeloid neoplasms with germ line *GATA2* mutation
Myeloid neoplasms associated with bone marrow failure syndromes
Juvenile myelomonocytic leukemia associated with neurofibromatosis, Noonan syndrome, or Noonan syndrome-like disorders
Myeloid neoplasms associated with Noonan syndrome
Myeloid neoplasms associated with Down syndrome[†]
Guide for molecular genetic diagnostics[‡]
Myelodysplastic predisposition/acute leukemia predisposition syndromes
CEBPA, *DDX41*, *RUNX1*, *ANKRD26*, *ETV6*, *GATA2*, *SRP72*, 14q32.2 genomic duplication (*ATG2B*/*GSKIP*)
Cancer predisposition syndromes[§]
Li-Fraumeni syndrome (*TP53*)
Germ line *BRCA1*/*BRCA2* mutations
Bone marrow failure syndromes
Dyskeratosis congenita (*TERC*, *TERT*)
Fanconi anemia

[*] *Recognition of familial myeloid neoplasms requires that physicians take a thorough patient and family history to assess for typical signs and symptoms of known syndromes, including data on malignancies and previous bleeding episodes.*
[†] *Lymphoid neoplasms are also reported.*
[‡] *Molecular genetic diagnostics are guided by a detailed patient and family history; diagnostics should be performed in close collaboration with a genetic counselor; patients with a suspected heritable myeloid neoplasm, who test negative for known predisposition genes, should ideally be entered on a research study to facilitate new syndrome discovery.*
[§] *Mutations in genes associated with cancer predisposition genes such as TP53 and BRCA1/2 appear to be frequent in therapy-related myeloid neoplasms.*

Table 2.
WHO classification of myeloid neoplasms with germ line predisposition and guide for molecular genetic diagnostics.

Affected patients, including their families, should benefit from genetic counseling with a counselor familiar with these disorders.

4. European leukemia net 2017 recommendations

The WHO 2008 and 2016 classifications incorporated modifications that allowed for a greater number of patients to be classified into the category of AML [28]. However, in 2010, an international expert panel, on behalf of the European

Leukemia Net (ELN), established recommendations for diagnosis and management of acute myeloid leukemia. These recommendations have been widely used in practice, within clinical trials, and by regulatory agencies. Recently, a big progress has been made in understanding disease pathogenesis and in the development of diagnostic assays and novel therapies. The ELN recommendations were updated, and new recommendations were published.

The goal of ELN is to subdivide genetic categories on prognostic groups to make easier correlations between genetic abnormalities and clinical characteristics and outcomes.

Although a subsequent study elicited a longer overall survival (OS) in the intermediate I group than in the intermediate II group, both groups were prognostically indistinguishable in the more aged patients, who represent the majority of AML cases [25].

The new recommendation of ELN identifies three groups (favorable, intermediate, adverse) with some changes. It was proved that in AML with NPM1 or biallelic CEBPA mutations, the presence of coexisting chromosomal abnormalities does not appear to modify the prognostic [29].

The latest published research has confirmed that the relapse rate and outcomes associated with FLT3-ITD are related to the ITD allele ratio. Studies showed that patients with NPM1 and FLT3-ITD mutation with a low allelic ratio (<0.5) (FLT3-ITDlow) have the same response rate as patients with NPM1 mutation but no FLT3-ITD; they are classified in the favorable group.

The latest findings from recent research suggest that the presence of the FLT3 mutation alone is not sufficient to classify patients into unfavorable prognostic groups and that patients with a NPM1 and FLT3-ITD mutation with a low allelic ratio (<0.5) (FLT3-ITDlow) have the same result as patients with a NPM1 mutation without FLT3-ITD; they are included in a favorable group [30, 31].

Patients with a high ratio are classified in the unfavorable group when they have wild-type NPM1 and FLT3-ITD with a high (>0.5) allelic ratio ($FLT3\text{-}ITD^{high}$); those patients have a poor outcome, but recently the use of FLT3 inhibitors can improve prognosis [32].

Other abnormalities were introduced to adverse-risk group like RUNX1, ASXL1, and TP53 mutations and monosomal karyotype [33, 34].

5. Medical Research Council (MRC) cytogenetic classification

In the past Medical Research Council (MRC) cytogenetic classification was developed, by analyzing a cohort of 1612 children and younger adults (55 years) treated in the MRC AML10 trial; this work was realized more than a decade ago and distinguishes three cytogenetic risk groups [35]. The first group includes patients with t(15;17), t(8;21), and inv(16), irrespective of the presence of additional cytogenetic changes; these categories were assigned to the "favorable-risk" group. The 2sd group concerns patients who have none of these aberrations and who have abn(3q), del (5q), 5/7, or complex karyotype (five or more unbound cytogenetic abnormalities). This group was considered as an "adverse risk." Other patients, those with normal karyotype (NK) and other structural or numerical abnormalities, were in the "intermediate-risk" group. In the original MRC study, patients having infrequent or rare abnormalities were not considered individually and were assigned to the intermediate-risk group [36].

Advances in molecular biology have provided important insights into molecular abnormalities that previously were poorly understood.

Significant advances in technology, including chromosome banding, with fluorescence/chromosome in situ hybridization, or other analyses like array comparative network genomic hybridization, genome breakpoints cloning and Sanger sequencing of candidate genes and profiling of single nucleotide polymorphism, and even whole-genome sequencing (WGS), whole-exome sequencing (WES), and RNA sequencing have all contributed to incremental improvements in understanding the genetic basis of the AML.

The whole-genome sequencing for AML confirmed that it is a complex and instable disease. There are many leukemia genes, most of which are infrequently mutated, and patients typically have many driver mutations. The evolution is characterized by emergence of many competing clones which can coexist at any time.

Figure 1 illustrates different genes and clones coexisting in the same patient [17].

The Cancer Genome Atlas (TCGA) consortium analyzed 200 AML patients by whole-genome or whole-exome sequencing and identified 23 genes as "significantly mutated" at a higher-than-expected frequency [37].

Recently research confirmed that normal karyotype AML is a very heterogeneous group; many gene mutations were detected in normal karyotype AML by cutting-edge next-generation sequencing NGS technology, like FLT3-ITD, NPM1, CEBPA, and other additional mutations.

DNMT3A and RUNX1 mutations represent the most important predictors of shorter overall survival in AML patients aged less than 60 years and particularly in those with intermediate-risk cytogenetic. NPM1 mutations in the absence of FLT3-ITD, mutated TP53, and biallelic CEBPA mutations were identified as important molecular prognosticators of OS irrespective of patient age. Researching these gene mutations is important. It can be helpful on diagnosis and it can be a molecular marker of prognosis, predictive for response of treatment, and used also for disease monitoring.

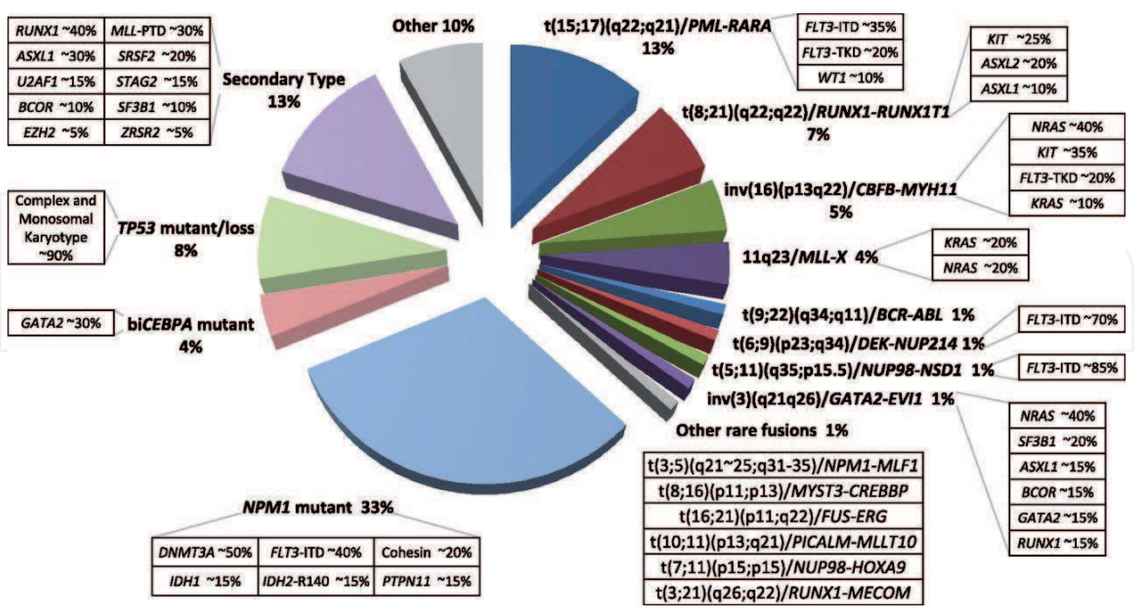

Figure 1.
Molecular classes of AML and concurrent gene mutations in adult patients up to the age of ~65 years. For each AML class denoted in the pie chart, frequent co-occurring mutations are shown in the respective boxes. Data on the frequency of genetic lesions are compiled from the databases of the British Medical Research Council (MRC) and the German-Austrian AML study group (AMLSG) and from selected studies. It indicates cohesin genes including RAD21 (10%), SMC1A (5%), and SMC3 (5%); inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11; and inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1), and TP53 mutations are found in 45% and complex karyotypes in 70% of this class.

It has been proven in previous studies that patients with cytogenetically normal AML or intermediate-risk abnormalities have more additional gene mutations than patients with favorable or unfavorable abnormal cytogenetic and especially those with balanced translocations [38].

Elderly patients have more driver gene mutations than younger patients. Older patients are characterized by having more alterations in specific genes including TET2, RUNX1, ASXL1, and SRSF2. All this genes have recently been implicated in age-related clonal hematopoiesis. These data contribute to highlight our understanding of differences in AML biology between younger and older patients [39].

5.1 Mutations in the fms-related tyrosine kinase 3 gene (*FLT3*)

Mutations in the fms-related tyrosine kinase 3 gene (*FLT3*) are present in 30% of patients having AML [40]. In approximately three quarters of these patients, the mutation found concerns *FLT3* internal tandem duplication mutation (ITD subtype). This mutation is the result of the duplication between 3 and more than 100 amino acids located in the juxtamembrane region. Studies confirmed that patients with AML having ITD mutations had a poor outcome with high risk to relapse. The rate of response is related to the ratio of mutant. In fact, the prognosis is poorer when there is a high ratio of mutant to wild-type *FLT3* alleles. This permits the development of specific treatment of such FLT3 inhibitors.

In fact, recent studies showed that the use of several specific tyrosine kinase inhibitors improves outcome and clinical trials that are underway [41, 42]. The inclusion of such inhibitors in therapeutic strategy with alloHCT might further improve future outcome of patients with FLT3-ITD AML [43].

5.2 Nucleophosmin protein mutation

NPM1 mutation is detected approximately in 30% of cases of AML with normal karyotype NPM; it is an aberrant cytoplasmic localization of the nucleoplasmin protein. Nuclephosmin protein mutation also named as B23 or numatrin, is a nucleocytoplasmic shuttling protein that constantly exchanges between the nucleus and cytoplasm [44].

5.3 CCAAT/enhancer-binding protein alpha mutations

CCAAT/enhancer-binding protein alpha mutations in AML are associated with favorable prognosis and are divided into N- and C-terminal mutations (double-mutated). CEBPA mutation occurs in 5–10% of cases of acute myeloid leukemia. Recent studies have shown that CEBPA-double-mutated (CEBPA-dm) cases, rather than single mutants, are associated with a common gene expression signature and a relatively favorable outcome. Based on these features, CEBPA-dm AML has been recognized as a separate entity in the revised World Health Organization 2016 classification [45].

5.4 Recurrent mutations in isocitrate dehydrogenase 1/2 (IDH1/IDH2)

Recurrent mutations in isocitrate dehydrogenase 1/2 (IDH1/IDH2) occur in ~12% of patients with acute myeloid leukemia with normal karyotype. Mutated IDH2 proteins neomorphically synthesize 2-hydroxyglutarate resulting in DNA and histone hypermethylation, which leads to blocked cellular differentiation. The incidence of this gene mutation increases with age [46]. Enasidenib (AG-221/CC-90007) and ivosidenib (AG-120) are first-in-class, oral, selective, small-molecule inhibitors of IDH2- and IDH1-mutant enzymes, respectively.

5.5 DNMT3A mutation

DNA methyltransferase (DNMT) 3A catalyzes the addition of methyl groups to the cytosine residue of CpG dinucleotides in DNA; the role of DNMT3A is to encode the DNMT. DNMT3A is constituted by three main structure domains: an ATRX, DNMT3, and DNMT3L-type zinc finger domain, a proline-tryptophan-tryptophan-proline domain, and the methyltransferase (MTase) domain.

The proline-tryptophan-tryptophan-proline domain targets the enzyme to nucleic acid, whereas the zinc finger domain is responsible of mediating protein-protein and interacting with the transcription factors Myc and RP58, the heterochromatin protein HP1, histone deacetylases, and the histone methyltransferase Suv39h1 [47].

DNMT3A mutation confers a specific clinical and biological feature, it is associated with poor prognostic, and it represents an unfavorable risk factor in AML patients independent of others risks factors like age, WBC counts, karyotype, and other genetic markers.

6. Conclusion

The update of WHO classification and ELN recommendations is useful for physicians; it can help to better subdivide risk groups and propose adequate treatment for each group [28]. On the other hand, an increasing understanding of molecular aberrations that triggers the development of AML and growing use of next-generation sequencing are advancing the development of investigational drugs against potential driver mutations in AML.

Conflict of interest

The authors declare no conflict of interest.

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