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Cytogenetic abnormalities in adult non-promyelocytic acute myeloid leukemia: A concise review

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Contents

Abstract

Cytogenetic abnormalities are found in 50–60% of newly diagnosed acute myeloid leukemia (AML) of adult patients. Cytogenetic analysis of bone marrow leukemic cells is an important pre-treatment evaluation for a correct prognostic stratification of patients, that permit to separate

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AML patients in three broad prognostic categories: high, intermediate and low risk. The determination of cytogenetic features of AML remains a corner stone in predicting outcome although today its use needs to be integrated by molecular and immunophenotypic data, particularly in cytogenetically normal (CN) group of patients.

In this review we perform a concise description of more recurrent cytogenetic aberrations found in AML, theirs correlations with biological and clinical data and theirs strong impact with outcome of patients, useful for therapeutic decision.

Keywords: Acute myeloid leukemia; Cytogenetic abnormalities; Cytogenetic risk; Prognostic stratification

1. Introduction

Cytogenetic abnormalities are identified in 50–60% of newly diagnosed acute myeloid leukemia (AML) of adult patients [1–6]. Pre-treatment evaluation directed to stratifying risk classes of patients includes also cytogenetic evaluation of bone marrow. Cytogenetic analysis more than age, white blood cell count, presence of an antecedent hematological disease and performance status is the most important factor to stratify AML patients into groups at low, intermediate and high risk [7]. Furthermore, in newly diagnosed AML patients with abnormal karyotype, cytogenetic analysis is recommended also for documenting complete remission (CR) [8]. In fact, several data show that the persistence, after induction chemotherapy, of cytogenetic abnormalities present at diagnosis in leukemic blasts determine an high relapse rate of leukemia and a worse clinical outcome with lower disease-free survival (DFS) rate and overall survival (OS) [9].

Therefore, the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia has introduced into standard response criteria for AML the category of cytogenetic CR defined as the absence of any cytogenetic aberrations in bone marrow leukemic blasts after induction chemotherapy in presence of morphologic CR and complete peripheral hematological recovery (Table 1) [7,8].

Cytogenetic analysis at diagnosis is today the most important prognostic factor in predicting outcome of AML patients. Stratification of AML patients according to cytogenetic assessment permits to establish the best post-remission therapy for single patient. In particular, high risk cytogenetics patients are potential candidate for an allogeneic hematopoietic stem cells transplantation (HSCT), whereas low risk cytogenetics patients will receive only standard chemotherapy [10]. It remains to be defined which is the best treatment for intermediate risk AML patients.

2. Cytogenetic-risk classification

Although there are some differences in the classification of cytogenetics risk based on karyotype results among the various cooperative international groups, AML patients are generally classified into three groups: high, intermediate and low risk [2,3,6].

The more used proposed classification is summarized in Table 2 [11].

Two important multicenter clinical trials of the Cancer and Leukemia Group B (CALGB) [3] and of the United Kingdom Medical Research Council (MRC) [6] demonstrated the importance of initial cytogenetics assessment on outcome of patients with AML, showing important differences in DFS and OS between high, intermediate and low cytogenetic risk groups. In particular Byrd et al. [3], in a large retrospective analysis of 1213 AML patients aged 15–86 years (median age: 52 years), of whom 18 (2%) were of acute promyelocytic leukemia, showed an estimated probability of 5-year OS of 55%, 24% and 5% in low, intermediate and high risk AML patients respectively. Similar results were obtained by Grimwade et al. [6] in an analysis of 1612 AML patient with median age of 35 years suggesting a 5-year OS of 61%, 42% and 4% in patients with inv(16), normal karyotype and complex karyotype respectively.

The classifications about cytogenetic risk groups in AML patients are based on studies predominantly including younger patients (aged <60 years) [3,4,6].

Two other studies of the same cooperative groups [2,12] demonstrated that also in elderly AML patients, cytogenetic features of bone marrow blasts at diagnosis are a real and independent prognostic factor. However, there are important differences between the prognostic significance of some cytogenetic aberrations between younger and older patients. The above two studies have shown that the clinical outcome of older patients with complex karyotype is particularly unfavourable (5-year DFS and OS: 0%) [2,12]. These data confirm that cytogenetics characterization at diagnosis in AML patients needs to complete with clinical factors and that age is probably the most important additional prognostic factor able to predict clinical outcome of these patients. A comparison of clinical data of different multicenter trials of international cooperative groups was described in Table 3.

It is important to consider that the largest subset of AML patients is represented by a group in which it is impossible to identify cytogenetic aberrations. Patients with normal karyotype at diagnosis are generally classified in intermediate risk group [3–6]. However, this group of patients is characterized by a notable heterogeneity in clinical outcome, showing a different response to treatment. For this reason, molecular characterization is very important particularly in this subset of AML patients [11,13].

Table 1
Response criteria after treatment in AML (adapted from [8]).

Response criterion	Neutrophils (μL)	Platelets (μL)	Bone marrow blasts (%)	Other
Morphological CR	>1.000	>100.000	<5	No EMD
Cytogenetic CR	>1.000	>100.000	<5	Normal cytogenetics, no EMD
Molecular CR	>1.000	>100.000	<5	Molecular biology negative, no EMD
Partial remission (PR)	>1.000	>100.000	5–25	–

EMD: extramedullary disease.

Table 2
The most used cytogenetic-risk classification in younger adult with AML (adapted from [11]).

High-risk group	Complex karyotype
Balanced structural rearrangements	inv(3)(q21;q26) t(3;3)(q21;q26) t(9;22)(q34;q11) t(8;16)(p11;p13) inv(8)(p11;q13) t(6;9)(p23;q34) t(6;11)(q27;q23) t(11;19)(q23;p13.1-3)
Unbalanced structural rearrangements	del(5q)
Numerical aberrations	-5 -7
Intermediate-risk group	Normal karyotype
Balanced structural rearrangements	t(9;11)(p22;q23)
Unbalanced structural rearrangements	del(7q) del(9q) del(11q) del(20q)
Numerical aberrations	+8 +11 +13 +21
Low-risk group	
Balanced structural rearrangements	inv(16)(p13;q22) t(16;16)(p13;q22)[a] t(8;21)(q22;q22)[a]

[a] In absence of KIT mutations.

3. High cytogenetic-risk AML

3.1. Complex karyotype

Complex karyotype is defined by the presence of 3 or more cytogenetic abnormalities in bone marrow not including inv(16), t(16;16), t(8;21), t(15;17) and t(9;11) [3,6,14–17]. As a consequence, some studies do not include in the complex karyotype category AML patients having at diagnosis t(9;21)(p22;q23) [3,12], any balanced rearrangements involving band 11q23 or any primary balanced abnormality [18,19].

The estimated incidence of complex karyotype in AML patients is about 10–12% [2,4,15] and it is now clear that this incidence increase with age: the MRC multicenter study showed the presence of 5 or more chromosomal aberrations in

Table 3
A comparison of the clinical data obtained in AML by different cooperative groups worldwide according to cytogenetic risk.

Cooperative study group	No. of patients	Median age (range)	Year of publication	CR (%) by risk group			5-year OS (%) by risk group		
				Low	Inter	High	Low	Inter	High
CALGB 8461 [3]	1213	52 (15–86)	2002	88	67	32	55	24	5
MRC AML10 [6]	1612	35 (na)[a]	1998	87–98	75–91	42–67	65	41	14
SWOG/ECOG [4]	609	na[a] (16–55)	2000	84	76	55	55	38	11
AMLSG AMLHD98-B [18]	361	67 (61–84)	2006	80	53	19	38[b]	18[b]	5[b]
GIMEMA LAM99P [101]	509	46 (15–60)	2008	92	67	39	na[c]	na[c]	na[c]

CALGB: Cancer and Leukemia Group B; MRC: Medical Research Council; SWOG/ECOG: Southwest Oncology Group/Eastern Cooperative Oncology Study Group; AMLSG: German-Austrian AML Study Group; GIMEMA: Gruppo Italiano Malattie EMatologiche dell'Adulto.

[a] na, not available.

[b] OS (%) is limited to 3 years.

[c] Not available data about OS.

In this study the 2-year DFS was 71% in low risk group, 52% in intermediate risk group and 32% in high risk group.

6% of AML patients aged under 55 years (including children) and in 13% of AML patients older than 55 years [2]. A second study found the presence of a complex karyotype in 18% of AML patients aged 60 years and above [20].

Complex karyotypes are more common in secondary AML (approximately twice as common than in de novo AML), causing the progressive accumulation of chromosomal aberrations determining by antecedent alkylant treatment, radiotherapy or other hematologic disease [2,21].

Although complex karyotype is defined as the presence of 3 or more chromosomal aberrations, the majority of patients is characterized by a high number of aberrations, that in some patients may reach the number of 30 [15,22].

The presence of complex karyotype aberrations in bone marrow blasts of AML patients correlates in all patients with a poor prognosis, low response rate to intensive induction treatment, high relapse rate, worse DFS and OS [3,4,6].

In patients aged >60%, who represent the majority of AML patients with a complex karyotype, the complete remission (CR) rate is very low and in different studies [12,18,20] only 10–40% of patients achieved CR after conventional intensive induction treatments. In the majority of cases the disease is resistant to first-line treatment. Almost all patients who are able to achieve CR experience an early relapse (median duration of CR: 6–8 months) and the 3-year OS is between 0 and 6% [2,12,18,20]. In patients aged between 18 and 60 years CR rates are slightly higher, with a slightly better DFS and OS compared to elderly patients. In two large studies, CR rates of 37 and 47% respectively have been reported associated to a 3-year OS rates of 3 and 12% respectively [4,20]. As for pediatric patients with complex karyotype, despite they may achieve a high CR rate of 75–78%, a high relapse rate has also been reported with a 3-year OS ranging from 19 to 36% [23,24].

As suggested by some studies [25,26], an allogeneic HSCT is able to improve the clinical outcome of AML patients with complex karyotype; however, this procedure is available only for a minority of AML patients, even though recent developments of reduced intensity conditioning (RIC) regimens in allogeneic HSCT have extended this possibility to patients aged >60 years. Recently Blum et al. described four case of CR (of low duration) in elderly AML patients treated with decitabine, a DNA demethylating agent, in a phase I trial evaluating this new anti-leukemic agent alone or combined with valproic acid [27]. Only few reports in medical literature suggest a possible relation between the type of detected aberrations present in a complex karyotype and the clinical outcome. Slovak et al. demonstrated that the presence of chromosomal aberrations involving chromosome 5 or 7 (-5/5q- and/or -7/7q-) determine a reduced CR rate and OS in AML patients treated with standard therapy comparing to patients with complex karyotype not including these alterations [4] and similar results have been suggested also by other investigators.

3.2. inv(3) and t(3;3)

Rearrangements of the long arm of chromosome 3 as the paracentric inversion of chromosome 3 [inv(3)(q21;q26)] and the translocation between the long arms of both homologous chromosomes 3 [t(3;3)(q21;q26)], are found in approximately 2.5% of AML [3,4,6]. These cytogenetic aberrations have also been observed in myelodysplastic syndrome (MDS) and in megakaryoblastic crisis of chronic myeloid leukemia (CML) [28].

The chromosomal breakpoints in 3q26 are scattered over several hundred kilobases in the region of EVI1 (Ecotropic Viral Integration Site 1) gene [29]; in the 3q21 region the chromosomal breakpoints are restricted to a smaller DNA region (100 kilobases) that encode for RPN1 (Ribophorin 1) gene. The leukemogenic effect of 3q21q26 rearrangements has been suggested to be due to the ectopic expression of EVI1 gene by the gene RPN1 acting as an enhancer of EVI1 expression [30]. It is very interesting that this mechanism is described mainly in lymphoid leukemias and lymphomas but more rarely in leukemogenesis of myeloid malignancies.

The EVI1 protooncogene codes for a DNA binding zinc finger protein acting as a repressor or activator of transcription; EVI1 is inappropriately expressed in leukemic cells after rearrangements of the 3q26 chromosome band and several studies suggested that its ectopic expression in immature hematopoietic cells interferes with erythroid and granulocytic development [28].

AML patients showing at diagnosis these chromosomal aberrations present peculiar clinical features such as: frequent anemia, white blood count (WBC) normal or increased, an elevated or normal platelets (PLTs) count. The bone marrow cytology of these AML is characterized by a multilineage involvement, with erythroid and megakaryocytic dysplasia and the presence of micromegakaryocytes. Clinical outcome is very poor, with a low response rate to induction chemotherapy, early relapse and short-term DFS and OS [28,31].

In a study of the United Kingdom Cancer Cytogenetic Group a cohort of 66 patients with AML and abnormalities of chromosome 3 has been analyzed, showing a poor prognosis with an OS rarely exceeding 12 months despite an aggressive induction therapy [32].

Testoni et al. analyzed morphologic and clinical features of 10 homogeneous AML patients with inv(3) or t(3;3) [33]. The median age of this patients was 43.5 years, 9 of 10 patients were defined as FAB-subtype M1 and only one M2, WBC count was decreased in 5 cases and increased in other 5, median platelets count was 172×10^9/L (range: $55–440 \times 10^9$/L). A previous myelodysplastic syndrome (MDS) was observed in 3/4 cases (75%) of patients with t(3;3) and 2/6 cases (33.3%) with inv(3). All patients were treated with different lines of intensive chemotherapy even though clinical course and outcome were extremely poor: 9/10 patients were resistant to the first course of induction therapy and 6/10 patients died within 9 months from the diagnosis of AML, the median OS was of 9 months.

3.3. t(6;9)

The translocation involving the band 23 of the short arm of chromosome 6 and band 34 of the long arm of chromosome 9 [t(6;9)(p23;q34)] is found in 0.5–4% of cases of AML [3,4,6,31,34]. Historically this chromosomal aberration has been related to FAB-subtype M2 with bone marrow and peripheral blood basophilia, but more recent evidences have showed the presence of t(6;9) also in bone marrow blasts of FAB-subtype M1 or M4 with or without basophilia.

The translocation t(6;9) results in a chimeric fusion gene between the genes DEK, localized in short arm of chromosome 6 (6p23), and CAN or NUP214, localized at band 34 of the long arm of chromosome 9 (9q34). CAN gene physiologically encodes a nuclear pore complex protein that permits the correct transfer of messenger RNA and different proteins between nucleus and cytoplasm. The fusion gene determine an over expression of CAN gene, leading to leukemogenesis trough alteration of nuclear transport of various proteins resulting in a block of cell cycle in G_0 phase [34,35]. The breakpoints in DEK and CAN are clustered in introns, permitting detection of DEK-CAN fusion transcripts with molecular techniques such us qualitative polymerase chain reaction (PCR) or Southern blotting.

Today it is possible non only to detect but also to quantify levels of DEK-CAN transcripts with molecular technique of real-time quantitative PCR to monitoring the molecular response to treatment: the disappearance of DEK-CAN molecular transcript in bone marrow of an AML patient in CR after treatment correlates strongly with survival [35].

It seems that the presence of this translocation between chromosome 6 and 9 with the consequent formation of chimeric DEK-CAN fusion gene is responsible for the poor prognosis of this subset of AML patients; however it is worth noting that some studies have demonstrated a high (70–85%) prevalence of *fms-related tyrosine kinase 3 internal tandem duplication* (FLT3-ITD) mutation among patients with t(6;9) AML [31,36–38]. FLT3 gene is involved in processes of proliferation and differentiation of hematopoietic stem cells and its more frequent mutation ITD is detected in almost 30–40% of adult AML patients, leading to a worse clinical outcome. Therefore, it is difficult to know which alteration is really responsible of the poor prognosis of these patients.

AML patients with t(6;9) are young (median age 23 years) and most frequently present a de novo acute leukemia than a secondary form: however, some of the patients with are characterized by a previous exposition to toxic agents (i.e. chemotherapy or radiotherapy) or by a previous history of MDS. At diagnosis the WBC is generally lower than that seen in other AML and anemia and thrombocytopenia are frequently of grade severe; the bone marrow is usually hypercellular with the presence of myeloid blasts showing Auer rods of cytoplasmatic granules. Two adjunctive morphologic characteristics are: a multilineage dysplasia and a bone marrow basophilia. In the only large retrospective study on this form of AML, performed by a collaboration among 5 cooperative USA groups, a prevalence of 44% of bone marrow basophilia and of 67% of myelodysplasia was reported [36]. Despite there is not general consensus about the immunophenotypic pattern of AML patients with this translocation, the more frequently reported immunophenotypic pattern was a positivity for CD9, CD13, CD33 and HLA-DR antigens, usually associated to a positivity for CD45 and CD38 and sometimes expressing immature markers as CD34 and Terminal deoxynucleotidyl transferase (TdT) [36,38,39].

Clinical course is very poor: CR is achieved with standard induction chemotherapy in about 50% of cases with a very short response duration and very high relapse rate. Median survival is <1 year from diagnosis. These patients are candidate to an allogeneic HSCT, the only therapeutic procedure able to determine an improvement in DFS and OS.

3.4. t(8;16) and inv(8)

The balanced translocation between the band 11 of the short arm of chromosome 8 and band 13 of the short arm of chromosome 16 [t(8;16)(p11;p13)] is a rare chromosomal abnormality detected in 0.5% AML generally of FAB-subtype M4, M5a and M5b [40].

Also in this case, AML with t(8;16) could be de novo or secondary to another hematological malignancies or to exposure to toxic agent (i.e. chemotherapy or radiotherapy for another neoplastic disease).

The gene involved in 8p11 rearrangement is MOZ (monocytic acute leukemia zinc finger), a gene of 17 exons currently named MYST3 (MYST histone acetyltransferase 3). MYST3 encode for a nuclear protein with an histone acetyltransferase activity, that acts as a transcriptional regulator [40]. The other gene most frequently involved in t(8;16) is CBP gene localized in the short arm of chromosome 16, that encode for CREB-binding protein (CREBBP). CREBBP is also a nuclear protein with acetyltransferase activity with a role of transcriptional control, determined by its interaction with DNA, essential in embryogenesis, cell differentiation, apoptosis and proliferation [41]. MYST3 rearrangements are also found in others translocations involving the chromosome 8 in AML such as: t(8;19)(p11;q13), t(8;22)(p11;q13), inv(8)(p11;q13) and t(8;20)(p11;q13) [42,43].

There are two forms of t(8;16) AML: the first more frequently described in pediatric patients, and the second more frequent in adult patients and secondary to another cancer, a previous chemotherapy or radiotherapy, or another haematological disease (i.e. chronic myelomonocytic leukemia). At diagnosis WBC is generally elevated with anemia and thrombocytopenia, extramedullary involvement, such as hepatomegaly, splenomegaly, adenopathy and skin localization, are frequent and disseminated intravascular coagulation (DIC) is classically observed. Gervais et al. reported a series of 30 AML patients with 8p11 rearrangement: at diagnosis a DIC was present in 12 cases (40%) [40]. Bone marrow smear reveals usually a hypercellular bone marrow with myelomonocytic, monoblastic or monocytic blasts, with fre-

quent cytoplasmatic vacuoles and peculiar presence of bone marrow erytrophagocytosis. Immunophenotypic analysis frequently shows positivity in bone marrow blasts for CD4, CD14, CD56, CD13, CD33, CD11, CD65, HLA-DR and CD15 and negativity for CD34 antigen [44,45].

Prognosis of this form of AML is very poor, with fatal clinical course despite intensive induction chemotherapy. Younger patients should be candidate to allogeneic HSCT.

The pericentric inversion of chromosome 8 [inv(8)(p11;q13)] is a rare chromosomal aberration found in few cases of patients affected by AML. Because the inversion involves one of the same bands as the t(8;16)(p11;p13) it can be consider as a variant of this translocation [46,47]. This pericentric chromosomal inversion determines the fusion of MYST3 gene with TIF2, a gene localized in the long arm of chromosome 8 that encode for a nuclear receptor coactivator capable to interact and to active CBP gene [48]. Clinical features of patients with inv(8) are similar to t(8;16) AML.

3.5. t(3;5)

The balanced translocation between the long arm of chromosome 3 and the long arm of chromosome 5 is a rare chromosomal aberration occurring in <1% AML patients and more frequently in MDS of young adults [2]. Variable breakpoints for this translocation are reported in the literature, but the breakpoints are most commonly described as t(3;5)(q25;q35) [49]. This chromosomal rearrangement leads to a fusion of the nucleophosmin gene (NPM, localized in chromosome 5) with myeloid leukemia factor 1 (MLF1) gene on chromosome 3. The NPM gene is involved in ALK-NPM fusion of anaplastic-large-cell lymphoma and a fusion partner with RARα in a small percentage of cases of acute promyelocytic leukemia; MLF1 is a gene normally expressed in various tissues. NPM/MLF1 fusion gene encode for a protein generally expressed in the nucleus and particularly in the nucleolus, binding the myeloid nuclear differentiation antigen, a nuclear protein important to development of human myelomonocytic cells [49,50]. It is not clear the real effect of this chimeric gene in the pathogenesis of MDS/AML; further studies are then needed to evaluate the prognostic role of t(3;5) and its role in leukemogenesis.

AML patients with t(3;5) generally are young (median age 36 years), characterized by multilineage dysplasia and associated to FAB-subtype M4 or M5. Prognosis is poor despite intensive chemotherapy for the high rate of relapse. For this reason AML patients with t(3;5) are possible candidates to allogeneic HSCT.

3.6. MLL rearrangements [t(6;11), t(11;19) and t(10;11)]

Aberrations in the band 23 of the long arm of chromosome 11 (11q23) occur in approximately 4–10% of AML patients [3,4,6]. Particularly 11q23 rearrangements is present in about 40–50% of childhood AML, 5% of adult de novo AML and 80% of adult secondary AML (i.e. in therapy-related AML, especially after treatment with topoisomerase II inhibitors) [51,52]. The 11q23 chromosomal aberration was described first in 1979 in patients affected by acute lymphoblastic leukemia (ALL). To date, more than 80 chromosome loci have been described as partner site of reciprocal translocations involving band 11q23 and the majority of these translocations involve the mixed-lineage-leukemia (MLL) gene. MLL is a gene of 36 exons, encoding a nuclear protein of 3969 amino acids that act as a positive regulator of gene expression in early embryonic development and hematopoiesis [53]; the exact function of MLL gene is actually unknown. Almost all the breakpoints in MLL gene occur in a 8.3-kb region, named breakpoint cluster region (BCR) and encompassing exons 8–14. In treatment-related adult AML the genomic breakpoints tend to cluster in the 3′ portion of BCR, near exon 12, whereas in adult patients with de novo AML tend to occur in the 5′ portion of BCR between exons 9 and 10 [54]. MLL gene translocations resulted in the production of a chimeric protein in which the amino-terminal portion of MLL gene is fused to the carboxy-terminal portion of the partner fusion gene: these gene fusions may alter the normal cellular differentiation processes, favouring leukemogenesis [55].

AML with 11q23 rearrangements, with the only exception of t(9;11) are characterized by poor prognosis and worse clinical outcome. The different sub-type of 11q23 AML rearrangements present similar clinical features at diagnosis as: frequent anemia, high WBC counts and thrombocytopenia, diffuse bone marrow infiltration by myeloid blasts and M2, M4 or M5 FAB-subtype and extramedullary disease in almost one third of patients. In the German Acute Myeloid Leukemia Intergroup study WBC count was significantly higher in AML patients with t(6;11) with a median WBC count of 55.5×10^9/L [56].

Moreover, some translocations are most frequently relate to peculiar clinical characteristics: t(6;11) is frequently associated to AML with multilineage dysplasia, whereas t(11;19) is typically associated to a biphenotypic leukemia.

11q23 AML are characterized by a lower CR rate and shorter DFS and OS. For this reason this setting of patient are considered as high risk AML patients and should be candidate to allogeneic HSCT.

The most common 11q23 aberrations are t(9;11), t(6;11), t(10;11) and t(11;19). Translocations involving chromosome 9 and 11 are described in another section of this review (i.e. intermediate cytogenetic risk AML).

3.6.1. t(11;19)(q23;p13.3)

The translocation between band 23 of the long arm of chromosome 11 and the band 13.3 of the short arm of chromosome 19 occur in 10–20% of all AML patients having 11q23 aberrations [50]. Although in a Japanese multicenter study t(11;19) was found in 14/52 11q23 AML patients (27.4%) at diagnosis [53], a recent meta-analysis of the German Acute Myeloid Leukemia Intergroup dealing with the prognostic significance of 11q23 aberrations in 180 AML adults aged <60 years has

found only 17 patients with a t(11;19), with an incidence of 9% [54]. The breakpoint in the MLL gene occurs within a 8.3-kb genome region, including exon 5 through 11. This alteration determines the formation of a fusion gene encoding for the chimeric protein MLL/ENL, acting as promoter of transcriptional processes and responsible of the leukemogenesis [57,58].

3.6.2. t(6;11)(q27;q23)

Translocation between band 27 of the long arm of chromosome 6 and the band 23 of the long arm of chromosome 11 occurs in about 15–20% of 11q23 AML patients. In the German study the incidence of this translocation was 19% in 11q23 AML patients aged less than 60 years [56].

The gene on chromosome 6 involved in this translocation is the AF6 gene, a 140 kilobases gene localized on chromosome 6q27 and composed by 32 exons.

The t(6;11) leads to formation of a fusion gene MLL-AF6 in which gene AF6 exon 2 is fused to exon 6 or 7 of MLL gene. This MLL-AF6 fusion gene is responsible of the leukemogenesis through the deregulation of HOX genes. HOX genes, normally regulated by MLL multiprotein complex, are important for the regulation of cell proliferation [59]; therefore, a deregulation of this gene determined by MLL-AF6 fusion gene contribute to leukemogenesis.

3.6.3. t(10;11)(p12;q23)

It represents about 5–8% of all 11q23 AML cases. This translocation involves MLL and AF10 genes, inducing the formation of MLL-AF10 chimeric gene. AF10 gene is localized on the short arm of chromosome 10 and encodes a 109-kDa protein. The real function of this protein is not known, but structural and functional data suggest its role as transcriptional factor [60].

Another translocation t(10;11)(p13;q14-21) not involving the MLL gene has been observed. In this translocation the genes involved are: the CALM (clathrin assembly lymphoid myeloid) gene is localized on chromosome 11q14-21 encoding a protein with multiple domains involved in endocytosis, the second gene is AF10, localized on chromosome 10p12-13. This translocation leads to formation of a chimeric gene CALM/AF10, responsible of the leukemogenesis by an unclear pathogenetic mechanism [60]. This translocation appears to be most frequently associated with T-cell ALL, specifically T-cell ALL of either γ/δ or immature phenotype and have also more rarely been observed in AML [60].

3.7. t(9;22)

Translocation between band 34 of the long arm of chromosome 9 and band 11 of the long arm of chromosome 22 [t(9;22)(q34;q11)] is found in about 1% of AML patients [4]. This translocation is identical to that observed in CML and Ph+ ALL and produces the fusion gene BCR-ABL that encode for the chimeric proteins p210 or p190, with high tyrosine-kinase activity.

It is difficult to establish whether or not a t(9;22) AML is a de novo AML or if it is a blastic phase of a precedent and unknown CML. Cytogenetic classifications of USA cooperative groups do not include t(9;22) in high risk AML, however in Italy AML with this chromosomal aberration are considered at high risk.

3.8. Monosomy and deletion of chromosome 7

Monosomy of the chromosome 7 (-7) and deletion of the long arm of the chromosome 7 (7q-) are found, as single chromosomal aberration, in approximately 4–5% of newly diagnosed AML.

In multicenter clinical trials of the Cancer and Leukemia Group B (CALGB) and of the United Kingdom Medical Research Council (MRC), the estimated incidence of these chromosomal aberrations was 7.8% among 1213 newly diagnosed AML patients aged 15–86 years and 6% among 1612 newly diagnosed AML patient with median age of 35 years respectively [3,6].

In a multicenter cooperative study of the Southwest Oncology Group/Eastern Cooperative Oncology Group (SWOG/ECOG), the incidence of -7 and 7q- in AML was 9% among newly diagnosed patients [4].

However, the incidence of these alterations is even higher when considered in the context of a complex karyotype. Brożek et al. in a series of 76 consecutive untreated AML found these chromosomal aberrations in 18% of cases, as single aberration or, more frequently, associated to others numerical or structural chromosome aberrations [61].

AML with chromosomal 7 aberrations represent a heterogeneous group; frequently are associated to others chromosomal aberrations, forming a complex karyotype. Monosomy 7 and deletion of 7q are present as single chromosomal alteration only in 35% and 33% respectively of all AML cases with chromosome 7 aberrations [62].

It is very important to remark that there is not universal agreement between the most important cooperative groups to classify AML with isolated deletion of chromosome 7 as unfavourable cytogenetic risk. In fact, in the cytogenetic risk classification proposed by Bloomfield and collaborators AML patients with deletion of chromosome 7 in absence of others structural and/or numeric chromosomal aberrations are considered as intermediate risk patients [11].

On the contrary, there is a total agreement about the negative prognostic impact of AML with -7, both as single or combined chromosomal aberration. A recent study of Dutch-Belgian Haemato-Oncology Cooperative Group and Swiss Group for Clinical Cancer Research highlights the very negative prognostic impact of monosomal karyotype in AML patients [63]. The term monosomal karyotype (MK) is used by authors for AML with at least two autosomal monosomies or one single autosomal monosomy in combination with at least one structural abnormality. A total of 987 newly diagnosed AML patients (between 15 and 60 years of age) with an abnormal karyotype were analyzed

in this study: in 63 patients an isolated -7 was found, with a negative prognostic impact (4-year OS: 13%). On the contrary, in others 49 patients -7 was found in the context of MK (i.e. or associated to others autosomal monosomies or as single autosomal monosomy with at least one structural abnormality) showing a stronger negative impact on clinical outcome (4-year OS: 0%). The authors conclude that MK (with or without -7) provides significantly better prognostic prediction than the traditionally defined complex karyotype in newly diagnosed AML [63].

Abnormalities in chromosome 7 are frequently associated to previous exposure to carcinogens or leukemogenic agents, in particular to alkylating drugs. In fact, these chromosomal aberrations are frequently found in MDS and their incidence is higher in secondary AML [61].

It is not fully understood which is the exact pathogenetic role of -7 and 7q- in leukemogenesis. So far, even though it has been hypothesized that in the long arm of the chromosome 7 is present an important tumor suppressor gene and some authors indicates the HIC (human I-mfa domain containing also called MyoD family inhibitor domain containing, MDFIC) gene as a possible candidate in leukemogenesis [64,65]; however, further investigations are necessary to evaluate the role of this gene in the development of AML.

Recent studies have shown the role of gene EZH2 in the pathogenesis of 7q- myeloid disorders. EZH2 gene encode the catalytic subunit of the polycomb repressive complex 2 (PCR2), a histone methyltransferase that influences stem cells renewal by epigenetic repression of some others genes: there are some evidences that mutations of EZH2 gene determine a direct or indirect abrogation of histone methyltransferase activity, acting as a tumor suppressor for myeloid malignancies [66,67].

AML patients with chromosome 7 aberrations are characterized by frequent multilineage dysplasia in bone marrow cells and worse clinical course with low rate of CR (20–30%) and low DFS and OS, particularly in AML patients with -7 or patients with 7q- in the context of a complex karyotype.

3.9. Monosomy and deletion of chromosome 5

Among newly diagnosed AML patients, monosomy of chromosome 5 (-5) and deletion of the long arm of the chromosome 5 (5q-) represents approximately 6–9% of all the chromosomal abnormalities [3,4,6].

Similarly to the aberrations of chromosome 7, these chromosomal alterations are frequently observed in patients previously exposed to alkylating agent or to other leukemogenic factor favouring multilineage dysplasia in bone marrow cells followed by MDS and finally by a secondary AML.

Also in this case, there is not general agreement among the international cooperative groups about how classify AML with chromosome 5 aberrations. Although -5 AML is universally considered an unfavourable cytogenetic risk, data are controversial for 5q- AML. In contrast to the cytogenetic classification proposed by Bloomfield [11], Byrd et al. have classified AML with isolated deletion of the long arm of the chromosome 5 in the intermediate cytogenetic risk group [3]. Similarly with -7 the presence of -5 in the context of a MK confers very poor prognosis (4-year OS: 0%) in newly diagnosed AML patients [63].

These chromosomal aberrations are frequently observed as sole chromosomal aberrations of MDS; whereas in AML these aberrations are more frequently associated with others cytogenetic abnormalities. In a recent study of the Group Francophone de Cytogénétique Hématologique (GFCH), 110 cases of AML/MDS selected on the base of the presence of chromosome 5 abnormalities revealed that -5 or 5q- were associated with others cytogenetic alterations in almost 54% of cases and only in 46% of cases were present as single chromosomal aberration.

The rate of detection of -5/5q- as single alteration was significantly lower when only patients with diagnosis of AML were considered. Alterations of chromosome 5 were associated with chromosome 7 abnormalities and more frequently (in 90% of cases) with a complex karyotype [68].

AML patients with chromosome 5 aberrations are characterized by frequent multilineage dysplasia in bone marrow cells and poor clinical course with low response rate to induction chemotherapy and high relapse rate.

4. Intermediate cytogenetic-risk AML

4.1. Normal karyotype

A normal karyotype, defined as the absence of clonal abnormalities detected in 20 or more fully analyzed bone marrow metaphase cells, is present in 40–50% of newly diagnosed AML [3,6,11,69]. It represents the largest cytogenetic subset of AML patients and is classified as intermediate risk by all the most important cooperative groups [3,4,6,7,11]. Normal cytogenetics AML is a heterogeneous group characterized by notable variability in terms of response to treatment, achievement of CR, relapse rate, DFS and OS. This is determined by a concomitant heterogeneity in molecular characterization of cytogenetically normal AML: in fact, during last decade, several studies have shown that the presence or absence of specific gene mutations and/or changes in gene expression affects the prognosis of AML patients. Molecular characterization of bone marrow blasts in newly diagnosed AML is a very important prognostic parameter in all cases and has a major significance for prognostic stratification of cytogenetically normal patients at diagnosis permitting a molecular risk-adapted treatment strategy, able to improve clinical outcome.

The gene mutations predominantly occurring in cytogenetically normal AML are summarized in Table 4 [69,70].

4.2. t(9;11)

The translocation between band 22 of the short arm of chromosome 9 and band 23 of the long arm of the chromo-

Table 4
Molecular characterization in cytogenetically normal (CN) AML (adapted from [70]).

Gene	Biological/clinical features
NPM1	Nuclear protein with oncogenic and tumour-suppressive function Found in 25–35% of AML and predominantly in CN AML Associated to favorable prognosis (in absence of FLT3-ITD mutations)
FLT3	Member of the class III receptor tyrosine kinase family Mutated gene leads to a constitutive activation of protein (leukemic transformation)
ITD	Found in 28–34% of CN AML Associated significantly to worse clinical outcome
TKD	Found in 11–14% of CN AML No clear prognostic impact; recently associated to better OS than ITD
MLL	PTD of MLL gene if found in 5–11% of CN AML Frequently associated to 11q23 rearrangements MLL-PTD found in 40–50% of AML with trisomy of chromosome 11 Associated with shorter CR duration, high relapse rate and lower DFS and OS
CEBPA	Transcription factor for differentiation of myeloid progenitors into neutrophilis Found predominantly in CN AML and in AML with 9q deletion Associated with higher CR rate and better DFS and OS
ERG	Nuclear target of signal transduction regulating and promoting cell differentiation High expression is associated with higher relapse rate and worse OS
BAALC	Physiologically expressed in hematopoietic precursors High expression is associated with worse clinical outcome
MN1	Fused with ETV6 in t(12;22) AML High expression of MN1 gene is found in CN AML High expression is associated with significantly inferior DFS and OS
c-KIT	Localized in chromosome 4, encode for a class III receptor tyrosine kinase family Found in about 30% of CBF AML and in rare cases of others AML types Mutations of c-kit gene is associated to worse clinical outcome
NRAS	Membrane-associated proteins regulating mechanism of differentiation and apoptosis Found in 9–14% of CN AML, in up to 40% of CBF AML and in 25% of inv(3) AML No clear impact of clinical outcome
WT1	Mutations of WT1 is found in 10% of CN AML No clear impact on clinical outcome; some data suggest lower CR rates

NPM1: mutations in nucleophosmin gene; FLT3: mutations of the fms-related tyrosine kinase 3 gene; ITD: internal tandem duplication; TKD: tyrosine kinase domain; MLL: mixed-lineage-leukemia gene; PTD: partial tandem duplication; CEBPA: mutations of the CCAAT/enhancer binging protein (C/EBP) alpha gene; ERG: v-ets erythroblastosis virus E26 oncogene homolog (avian) gene; BAALC: brain and acute leukemia cytoplasmic gene; MN1: meningioma 1 gene; WT1: mutations of Wilm's tumor 1 gene; NRAS: RAS viral oncogene homolog gene.

some 11 [t(9;11)(p22;q23)] is the most frequent translocation in AML having 11q23 aberrations, occurring in 30–40% of 11q23 AML [53,56].

This translocation causes a fusion between MLL gene, localized in chromosome 11, and AF9 gene, in chromosome 9. AF9 gene is greater than 110 kb and contains 10 exons: genomic analysis identified two different regions of breakpoint in AF9 gene involved in t(9;11), occurring in de novo or in therapy-related AML respectively [54,71,72]. The fusion gene MLL-AF9 leads to immortalization of hematopoietic progenitors and a monocytic differentiation block.

This chromosomal aberration is related to a peculiar clinical picture and outcome, differently to the others form of 11q23 AML: in particular, t(9;11) AML patients present frequently a younger age (median age of 38–40 years), a higher median value of hemoglobin and platelets count, extramedullary involvement, such as hepatomegaly, splenomegaly, adenopathy and skin localization and is frequently associated to M5 FAB-subtype [53].

It is now evident that this translocation has a better prognostic impact in clinical outcome of AML patients respect to all others chromosomal aberrations involving chromosome 11 and MLL gene, and for this reason it has been classified as intermediate cytogenetic risk by all international cooperative study groups [2,4,6,7]. In a recent meta-analysis analysing 180 adult patients (aged 18–60 years) with newly diagnosed AML having 11q23 abnormalities, the presence of t(9;11) was one of the only three factors having a positive prognos-

tic impact in the achievement of CR (the others two were: absence of adjunctive chromosomal aberrations and de novo leukemia), and one of the four favorable prognostic factors on OS together with de novo leukemia, platelets count higher than the median and peripheral blasts less than the median [56].

Therefore a correct stratification of AML with 11q23 abnormalities based on the translocation partners and on clinical parameters is very important for a correct definition of the prognosis of these AML.

4.3. Trisomy of chromosome 8

Trisomy of chromosome 8 (+8) is the most frequent numeric recurring aberration in AML and it has been reported both as single or combined alteration [3,4,6]. It is present as single chromosomal aberration in 6% of cases of newly diagnosed cytogenetically abnormal AML and it occurs in 10% of cases of cytogenetically abnormal AML cases as combined alteration [73]. This alteration appears to be typical of myeloid malignancies, considering its high prevalence in MDS and the possible expression in karyotype of patients affected by myeloproliferative disorders.

Some studies suggest that the incidence of +8 increases with age, being present in 11% of cytogenetically abnormal AML patients aged 81–90 years; other factors implicated in the increased incidence of this numeric aberration are: gender, geography-related differences and a precedent exposure to toxic agents [73,74].

However, it seems not associated with prior treatment with radiotherapy, alkylating agents or inhibitors of DNA topoisomerase II because it occurs more frequently in de novo AML. The pathogenetic role of +8 remains unclear; it has been suggested a possible role in the global over-expression of genes localized in chromosome 8. Some studies suggested that +8 can lead to a deregulation of the gene MYC, localized in band 24 of the long arm of the chromosome 8 (8q24) [75]. However this mechanism appears to be too simplistic because several studies have demonstrated that +8 is responsible of a deregulation of different genes; therefore, it is unlike that is represented by the up-regulation of a single gene [76] and microarray analysis shows that +8 seems to be associated with a global gene expression. Several data suggest that +8 AML has a heterogeneous gene expression profiling compared to AML with inversions or translocations [73]. It is now clear that +8 is not sufficient for leukemogenesis because it may also constitutional, occurring as a mosaicism (CT8M) in approximately 0.1% of pregnancies [77]. In this case the chromosomal aberration is the consequence of a postzygotic non-disjunction and clinical features of affected children are mild or moderate mental retardation, facial dysmoprphic alterations, bone and joint alterations and cardiovascular and uro-genital malformations. Individuals with CT8M have an increased risk for developing myeloid malignancies, that only in 5% will be MDS/AML with a latency of several years [78].

AML with +8 do not seem to have any clinical, morphological and immunophenotypic characteristics, except for a mild prevalence of M5a or M5b FAB-subtype.

As for the prognostic impact of +8 in AML, a meta-analysis of 131 patient aged 18–60 years with newly diagnosed AML and isolated trisomy of the chromosome 8 revealed the presence of three independent negative prognostic factors: age $\geq$45, the presence of extra-medullary disease and a percentage of +8 positive metaphases $\geq$80%. The 3-year OS was 13% for high risk sub-group, defined by the presence of all three characteristics, 36% for intermediate risk sub-group, defined by the presence of two over three characteristics, and 55% for the low-risk subgroup (only one of characteristics above mentioned) [79].

Trisomy 8 is considered by all the international cooperative groups as an intermediate cytogenetic-risk alteration [4,6,7,11]; only in the CALGB 8461 study +8 as isolated chromosomal aberration was classified in the high-risk category.

It is work noting that several evidences indicate that +8 occurring in association to others cytogenetic aberrations does not modify the prognosis of the associated alteration. In other words, the favorable prognostic impact of t(8;21), inv(16) and t(15;17) in AML is not modified by the presence of an additional +8.

4.3.1. Tetrasomy of chromosome 8

Tetrasomy of chromosome 8 is rarely observed in hematologic disorders. In the medical literature only 20 cases have been described so far [80]. It is more frequently present in M5 and M4 FAB-subtype AML and in some cases of MDS/AML and associated to a poor prognosis [80]. Considering its rarity, this chromosomal aberration is not included in cytogenetic classification of AML.

4.4. Trisomy of chromosome 11

Trisomy of chromosome 11 (+11) has been reported in both de novo and secondary AML or MDS and it is the third most common isolated chromosomal aberration found in de novo AML [81]; more frequently it is associated to others cytogenetic alterations.

AML with trisomy 11 do not appear to have peculiar clinical and immunophenotypic characteristics: Sierra and collaborators reported clinical and biological characteristics of 15/399 (4%) consecutive patients affected by newly diagnosed AML with trisomy 11 [82]. In this analysis median age of the patients was 68 years and only 1 patient was younger than 60 years, all patients presented anemia and thrombocytopenia at diagnosis and WBC was low in 8 of the 15 patients (median value was 9.5×10^9/L); bone marrow dysplasia is frequent and immunophenotypic analysis did not reveal a peculiar pattern but only a preferential involvement of early myeloid precursors. Clinical course of these patients was poor with a CR rate of 43% in patients treated with intensive chemotherapy and a median OS of only 2 months.

However, only 20% of these 15 patients presented an isolated trisomy 11 at diagnosis while the others 80% of the patients presented associated cytogenetic aberrations, such as trisomy 8, deletion of 5 and complex karyotype. Trisomy of chromosome 11 is frequently associated with partial tandem duplication of MLL gene. There is not univocal agreement about the real incidence of MLL mutations in trisomy 11 AML patients: the majority of studies shows an incidence of 40–50% [83,84]. These and others studies suggest that the concomitant presence of partial tandem duplication could be relevant in determining a subgroup of patients with trisomy of 11 having a worse clinical outcome.

The most important international cooperative groups are concord to consider AML with isolated trisomy 11 as intermediate cytogenetic risk category [3,6,11].

4.5. Trisomy of chromosome 13

Trisomy of chromosome 13 (+13) is a rare but recurring numeric chromosome alteration found as isolated aberration in 2.5% of newly diagnosed AML [3]. The molecular mechanism by which trisomy contribute to leukemogenesis is unknown, even though it has been reported to be correlated to over-expression of one or more gene localized in chromosome 13. FLT3 gene, localized in chromosome 13 and expressed in immature hematopoietic progenitors, is a good candidate for this deregulation: some evidences suggested the strong correlation between trisomy 13 with RUNX1 mutations and increased FLT3 expression in AML and two studies have recently demonstrated this correlation. In particular, Silva and collaborators analyzed 52 M0-AML patients among whom 16 patients presented a RUNX1 mutation (30.8%) and 8 carried a trisomy of 13 as non-isolated chromosomal aberration (15%). Of these 8 patients, 7 presented a mutation of RUNX1. In addition these 8 patients showed a 4-fold higher expression of FLT3 mRNA compared to controls confirming the correlation between trisomy 13 and high expression of FLT3 [85]. These results have been confirmed by Dicker et al. who, analysing 156 cases of newly diagnosed AML, demonstrated that trisomy 13 was the only isolated chromosomal aberration correlating with mutations of RUNX1 and with FLT3 expression [86].

Moreover, the great majority of studies dealing with trisomy 13 demonstrated the prevalence of this alteration in FAB M0-subtype.

Recently it has been shown that lenalidomide may have a potential activity in AML patients with trisomy 13 as isolated cytogenetic marker. In fact, Fehninger et al. have reported two cases of morphologic and cytogenetic CR achieved with high-dose lenalidomide in two older AML patients harboring trisomy 13 as sole chromosome abnormality [87]. Although the biologic mechanism of lenalidomide clinical activity in hematological malignancies is not fully understood, at present this drug is approved for treatment of relapsed multiple myeloma and of low-risk MDS with 5q-. Considering the high prevalence of trisomy 13 and FLT3 mutations, further studies are necessary to establish the potential targets of lenalidomide in AML.

Although does not exist a common agreement about the prognostic significance of trisomy 13, the tendency is to consider the presence of trisomy 13 an intermediate cytogenetic risk [11].

4.6. Trisomy of chromosome 21 (Down Syndrome)

The Down syndrome (DS) represents the most common human aneuploidy with an incidence of 1 in 700 births. With respect to hematopoietic system, children with DS frequently show macrocytosis, abnormalities in platelets count and an increased prevalence of leukemia [88]. The incidence of ALL in children with DS is approximately 20 times higher than in general population but the most frequent form of acute leukemia in DS children is the acute megakaryoblastic leukemia (AMKL, FAB-subtype M7 AML), with an incidence 500 times higher than general population.

AMKL is characterized by peculiar clinical and pathogenetic features with an excellent prognosis and an approximately 80% cure rate [88,89]. However, myeloid leukemias in people with DS aged 4 years or older does not differ (as clinical features and outcome) from AML in patients without DS.

The most important international cooperative groups on AML consider trisomy of chromosome 21 as an intermediate cytogenetic risk category [3,4,6,11].

5. Low cytogenetic-risk AML

5.1. t(8;21)

Translocation between band 22 of the long arm of the chromosome 8 and band 22 of the long arm of the chromosome 21 [t(8;21)(q22;q22)] is one the most common chromosomal aberrations occurring in adult patients with de novo AML, accounting for 7–8% of all aberrations [3]. This translocation leads to de-regulation of the core binding factor (CBF), a heterodimeric transcription factor involved in the regulation of the hematopoiesis. It is constituted by an α sub-unit, responsible of the link with DNA helix, and a β sub-unit, which facilitates this link [90,91]. The α sub-unit is encoded by AML1 gene whereas the β sub-unit is encoded by CBFβ gene. This translocation is characterized at molecular level by the fusion between gene AML1, mapped at band 21q22 and gene ETO, mapped at band 8q22 (AML1/ETO also called RUNX1/CBFA2T1). This fusion gene acts as a transcriptional repressor, blocking the normal processes of hematopoiesis.

AML with t(8;21) are frequently associated with specific clinical and biological characteristics represented by a typical morphology (M2 FAB-subtype) with myeloid precursors containing Auer rods, frequent high WBC count at diagnosis with frequent extramedullary localizations (granulocytic sar-

comas) and a peculiar immunophenotypic pattern expressing CD13, CD33, CD56 and an aberrant positivity of leukemic cells for CD19 [92].

It is interesting to note that t(8;21) sometimes it is associated to others cytogenetic aberrations, particularly the loss of sex chromosome, the deletion of the long arm of the chromosome 9 and trisomy 8.

AML with t(8;21) are characterized by a particularly favorable clinical outcome, with high CR rate, long CR duration and good OS, especially after high-dose cytarabine-based post-remission therapy [3,4,6,7,93–95]. In a large meta-analysis performed by the German Acute Myeloid Leukemia Intergroup 191/410 newly diagnosed CBF AML patient aged 16–60 years had t(8;21). CR in these 191 patients was achieved in 87% of cases with a 3-year DFS of 60% and a 3-year OS of 65%. In this meta-analysis the authors analyzed different prognostic factors potentially related to CR rate, DFS and OS: the only independent prognostic factors determining a negative impact on OS were platelets count $\leq 28 \times 10^9$/L, WBC count $\geq 25.4 \times 10^9$/L and loss of Y chromosome as adjunctive chromosomal aberration in male patients [17]. Similar results have been obtained by a CALGB study dealing with 144 consecutive AML patients with t(8;21) aged 17–75 years [14]. Among these 144 patients CR rate was achieved by 89% with a cumulative incidence of relapse at 5 years of 53% and a 5-year OS of 46%. Prognostic factors interfering negatively on OS were low platelets count, older age and the presence of del(9) as additional chromosomal aberration.

Therefore, the results of studies of the international cooperative groups suggest that patients with t(8;21) AML have not an improved outcome in terms of OS by using allogeneic or autologous HSCT and repetitive high-dose cytarabine-based courses are now universally considered the best post-remission therapy in this setting of patients [93–95].

However, some of these AML patients may have a more aggressive leukemic phenotypes independent from the clinical and cytogenetic prognostic factors mentioned above (i.e. platelets and WBC counts, age, additional chromosomal alterations); this behaviour suggests the presence of another factor able to influence the clinical outcome of CBF AML patients.

Several studies indicate that the mutated KIT gene is a good candidate to fulfil these criteria: the KIT gene is located in band 11–12 of the long arm of the chromosome 4, it encodes for a transmembrane glycoprotein member of the type III receptor tyrosine kinase family, and different types of mutations of this gene have been observed in CBF AML.

In a recent CALGB study 49 AML patients with t(8;21) were analyzed for two type of mutations of KIT gene (KIT17, on exon 17; KIT8, on exon 8): KIT mutations were found in 29.5% of patients. The study highlights that t(8;21) AML patients carrying mutation of KIT gene had a statistically significant higher cumulative incidence of relapse compared to patients with wild-type of KIT gene, although no difference in terms of OS was observed between the two groups [96].

5.2. *inv(16) and t(16;16)*

Pericentric inversion of chromosome 16 [inv(16)(p13q22)] and translocation between the short arm of chromosome 16 at band 12 and the long a arm of the same chromosome at band 22 [t(16;16)(p12q22)] are also common cytogenetic alterations recurring in de novo AML in 4–9% of cases [3,4,6,14,17].

Also these chromosomal aberrations lead to de-regulation of the core binding factor (CBF), determined by the fusion between CBFβ gene (located in 16q22 and encoding for the β sub-unit of CBF), and MYH11 gene (located in 16p13 and encoding for heavy chains of smooth muscle).

The breakpoints on CBFβ gene are localized at exons 5 or, more rarely, at exon 4; while the breakpoints in MYH11 gene are still unknown. The role of the fusion CBFβ/MYH11 gene in leukemogenesis is not clear, but it is possible that this gene could determine the oligomerization of CBFβ gene, leading to loss of its function and consequently loss of CBF function.

Inv(16) and t(16;16) are associated in 50% of cases to others chromosomal aberrations, more frequently to trisomy 8, 21 or 22 [3,17,97].

AML carrying inv(16) or t(16;16) are frequently associated to a peculiar morphologic presentation with FAB-subtype M4eo characterized by the presence of atypical eosinophils in bone marrow smear, and more rarely with FAB-subtype M5 or M2. Clinically AML with inv(16)/t(16;16) have been associated to high CR rate and favorable clinical outcome [3,6,95,98]. The large meta-analysis of the German Acute Myeloid Leukemia Intergroup revealed that among 201 with newly diagnosed inv(16)/t(16;16) AML aged 16 to 60 years, CR was achieved in 89% of cases with a 3-year DFS of 58% and a 3-years OS of 74%. In this study, high WBC count and advanced age were significantly associated to early death or death in aplasia [17].

Similar results were obtained by the CALGB study [14]: in this study among 168 consecutive AML patients aged 17–75 years with inv(16)/t(16;16), CR rate was 87% with a cumulative incidence of relapse at 5 years of 57% and a 5-year OS of 54%: prognostic factor able to impact negatively on CR rate and OS were older age and lower platelet count.

As indicated for t(8;21) AML, the presence of KIT gene had a negative impact on outcome with a significant lower OS also for inv(16) and t(16;16) AML [96].

Similarly to t(8;21) AML, allogeneic or autologous HSCT did not improve the OS of AML patients with inv(16) and t(16;16) and repetitive high-dose cytarabine-based courses are now universally recognized as the best post-remission therapy in this setting of patients.

6. Conclusions

Cytogenetic analysis at diagnosis is one of the most important prognostic factor in predicting outcome of AML patients. A correct assessment of cytogenetic risk in AML patients

Table 5
New risk-adapted classification of adult AML based on integration of cytogenetic and molecular data (adapted from [99]).

Genetic group	Subsets
Favorable	t(8;21) → AML1/ETO or RUNX1/CBFA2T1 inv(16)/t(16;16) → CBFβ/MY11 CN with mutated NPM1 in absence of FLT3-ITD CN with mutated CEBPA
Intermediate-I	CN with mutated NPM1 and FLT3-ITD CN with wild-type NPM1 and FLT3-ITD CN with wild-type NPM1 in absence of FLT3-ITD
Intermediate-II	t(9;11) → MLL-AF9 Cytogenetic abnormalities not classified as favorable or adverse
Adverse	Complex karyotype inv(3) or t(3;3) → RPN1-EVI1 t(6;9) → DEK-CAN or DEK-NUP214 MLL rearrangements -5 or del(5q) -7 or del(7q)

CN: cytogenetically normal.

permits the stratification of AML in different categories and the definition of the best post-remission therapy. Cytogenetic assessment is also a very important criteria for the evaluation of therapy response and the monitoring of residual disease post induction or consolidation treatment.

However, considering the low sensibility of some traditional cytogenetic tests and the relatively high prevalence of cytogenetically normal AML, molecular characterization of AML patients has rapidly grew in recent years.

Recently, considering the relevant impact on AML prognosis of some of the molecular markers, theirs importance on prognostic stratification and theirs utility on monitoring the minimal residual disease, an international expert panel, on behalf of the European Leukemia Net, has proposed a new classification on prognostic categories of newly diagnosed AML patients (see Table 5) as well as a standardized reporting system to correlate cytogenetic, molecular genetic and clinical data [99].

Moreover, several studies have proposed a dynamic and standardized method to monitor minimal residual disease also in cases of absence of a cytogenetic or molecular target. Maurillo et al have recently demonstrated that the level of minimal residual disease quantified by flow cytometry after consolidation therapy is able to predict the outcome in AML [100].

In conclusion, despite cytogenetic remains a corner stone for the prognostic stratification of AML patients its use in this setting needs to be integrated by molecular and immunophenotypic data.

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Conflicts of interest

All the authors declare the absence of any financial and personal relationships with other people and/or organisation that could influence the publication of this manuscript.

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