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16

New Molecular Markers in Acute Myeloid Leukemia

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1. Introduction

Acute leukemia is characterized by abnormal proliferation, inhibition of differentiation and expansion of leukemic cells blocked at the early stage of hematopoiesis. Acute myeloid leukemia (AML) is a malignant hematological disease of hematopoietic precursor cells of non-lymphoid lineage. Recent insights into the molecular mechanisms of AML are challenging the traditional diagnostic classification, prognostic significance and clinical practice of this hematological disorder.

1.1 Concept and classification

AML is a clinically heterogeneous disorder with distinct clinical and biological features. Until the 1970s, diagnosis was based on morphological examination of bone marrow and peripheral blood samples. In 1976, French, American, and British hematologists (the FAB group) defined six subgroups of AML morphological variants (Bennett et al., French-American-British Cooperative Group [FAB], 1976). This classification allowed us to identify several types of AML: M1-M6. Blastic populations were identified using standard staining techniques and consequently classified depending on reactivity to certain cytochemicals, namely, myeloperoxidase and Sudan black B (markers of myeloid differentiation) and nonspecific esterase reactions such as alpha-naphthyl acetate esterase and alpha-naphthyl butyrate esterase (for monocytic lineage). Later on, this group identified two new types of AML (M0 and M7) according to cytochemical and inmunophenotypical features (Bennett et al., FAB, 1985). Over the past decade, refinement in the diagnosis of subtypes of AML and advances in therapeutic approaches have improved the outlook for patients with AML (Döhner et al., 2010).

FAB classification
M0: AML minimally differentiated
M1: AML without maturation
M2: AML with maturation
M3: Acute promyelocytic leukemia
M4: Acute myelomonocytic leukemia
M5: Acute monoblastic leukemia
M6: Acute erythroleukemia
M7: Acute megakaryoblastic leukemia

Table 1. FAB classification of acute myeloid leukemia (AML).

Since several specific cytogenetic and genetic abnormalities in AML are associated with a characteristic morphology and have distinctive clinical behavior (Harris et al., World Health Organization [WHO], 1999). The World Health Organization (WHO), classification of myeloid neoplasms and acute leukemias integrates genetic, clinical data, and morphological features.

Three prognostic groups have been described classically according to cytogenetic findings. The favorable prognostic group includes the following chromosomal abnormalities: t(15;17), t(8;21) and inv(16). Normal karyotype and cytogenetic abnormalities not classified as favorable or adverse comprise the intermediate group. The adverse prognosis group includes patients with complex karyotype, del (5q), 5 or 7 monosomy, 3q abnormalities and t(6;9) (Dohner et al., 2010).

Recently the WHO published a revised and updated edition of the 1998 WHO classification where the importance of gene mutations as diagnostic and prognostic markers in myeloid neoplasms was acknowledged. This group recommended that fluorescence in situ hybridization (FISH), reverse transcriptase–polymerase chain reaction (RT-PCR) and mutational status studies should be guided through clinical, laboratory, and morphologic information. Mutational studies for mutated *NPM1*, *CEBPA*, *FLT3*, *KIT*, *WT1*, and *MLL* are recommended in all cytogenetically normal AML. Table 2 lists the major subgroups of AML in the WHO classification (WHO, 2009).

The genes involved in the pathogenesis of leukemia are normal genes (proto-oncogenes) with either structural alterations or deregulated expression patterns, which generates in turn a novel gene (an oncogene) whose protein product acts on the host cell to enhance malignancy-related characteristics. Oncogene activation and the loss of tumor-suppressor genes are consistently associated with some types of leukemia (Cline, 1994). Some of the molecular alterations involved in the pathogenesis of AML are: translocations, mutations and overexpression of normal genes, which often characterizes a particular subtype of AML. Therefore, there are also activating mutations which lead to increased proliferation or survival, or both, of haematopoietic progenitor cells through the stimulation of tyrosine kinases such as FLT3 or RAS family members. These are considered class I mutations (Haferlach et al., 2007; Schlenk et al., 2008). Class II mutations interfere with transcription and lead to a maturation arrest either through a direct alteration of transcription factors due to gene fusions (CBF-leukemias or PML-RARA positive leukemia) or by indirect interference with transcription (MLL-rearrangements). Cytogenetic and molecular analysis of leukemic blasts, provide critical diagnostic, therapeutic and prognostic information.

Acute myeloid leukemia with recurrent genetic abnormalities
AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
APL with t(15;17)(q22;q12); *PML-RARA*
AML with t(9;11)(p22;q23); *MLLT3-MLL*
AML with t(6;9)(p23;q34); *DEK-NUP214*
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
Provisional entity: AML with mutated NPM1
Provisional entity: AML with mutated CEBPA
Acute myeloid leukemia with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia, not otherwise specified
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Acute erythroid leukemia
Pure erythroid leukemia
Erythroleukemia, erythroid/myeloid
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm

Table 2. WHO classification of acute myeloid leukemia and related neoplasms.

1.2 Molecular markers

1.2.1 Useful at diagnosis and to evaluate Minimal Residual Disease (MRD)

Molecular techniques allow us to diagnose and classify AML, establishing groups of patients with different disease behaviour and prognosis. In the same way, the development of more specific therapies and the application of risk-adjusted therapeutic approaches have been made possible. Disease relapse can be favored by persistent low numbers of leukemic cells undetectable by conventional techniques. Monitoring of AML patients has given rise to a higher insight into the effectiveness of treatment. At diagnosis, some types of myeloid leukemias display a molecular change that might be useful as a marker of neoplastic disease and MRD (Hilden et al., 1995; Nakao et al., 1996; Foroni et al., 1999; Lo Coco et al., 1999a). Specific molecular alterations of certain hematologic malignancies are useful in the detection of MRD. Translocations are the most widely involved chromosomal abnormalities in AML. These can give rise to an altered function or activity of oncogenes located at or near the translocated breakpoint. The first molecular cytogenetic marker described in AML was t(15;17), which originates a single morphologic phenotype (hyper- or micro-granular French-American-British [FAB] AML-M3 acute myeloid leukemia) (Bernstein et al., 1980). This rearrangement disappears with complete remission and is able to predict a relapse very

accurately. The presence of this translocation or its fusion gene (PML/ RARα) is thus a detectable tumor marker in leukemic cells, which allows assessment of the molecular response to therapy in AML-M3 patients (Lo Coco et al., 1999b). *RUNX1-RUNX1T1* and CBFβ-MYH11 are other genetic alterations less likely to predict relapse, since they may persist even when complete remission (CR) has been achieved. However, the applicability of this strategy has been limited to those leukemia subsets characterized by genetic markers. Recent interest has focused on identifying new molecular markers that might prove significant in the diagnosis and follow-up of MRD in AML patients. In recent years, a variety ot potential molecular markers have been identified (see table 2 and table 3) (Radich & Thomson, 1997; Inoue et al., 1994; Kreuzer et al., 2001; Alberta et al., 2003; Lin et al., 2005; Gilliland & Griffin, 2002; Morishita et al., 1992).

Involvement of transcription				
	Prevalence	**Prognostic value**	**Associated mutations**	**Utility in MRD**
CBF-leukemias: Inv 16/t(16;16) CBFB/MYH11 t(8;21);*RUNX1-RUNX1T1*	15%	Favorable (Poor with KIT in normal karyotype leukemia)	FLT3 NRAS KIT	Possible
PML-RARA	10-15%	Favorable	FLT3 (40%)	Yes
MLL mutation	10-30%	Poor	-	Yes
CEBPA mutation	15-20%	Favorable if biallelic	-	Yes
AML1 mutation	1-20%	Poor	FLT3 (in 20% M0)	Yes
Activating mutations				
FLT3-ITD mutation	28-34%	Poor		Possible
FLT3-TKD mutation	20-30%	Controversial	CBF, NPM1	
c-KIT mutation	6-48%	Poor	CBF-leukemias	Yes
RAS mutation	NRAS 11% KRAS 5%	Not influence	FLT3-ITD (24-26%)	-
Other genes alterations				
NPM1 mutation	35%	Favorable (without FLT3)	FLT3	Yes
BAALC overexpression	65%	Poor	-	Possible
EVI-1 overexpression	10-22%	Poor	-	Possible
WT1 overexpression	10-15%	Poor	-	Yes
DNMT3A mutation	20%	Poor	FLT3-ITD	-
IDH1/2 mutation	15%	Controversial	NPM1, FLT3-ITD	-

Table 3. Molecular markers in AML: prevalence, prognostic, associated mutations, genetic alterations and utility in MDR.

1.2.2 Genetic alterations with prognosis value

In recent years, the availability of new genetic and molecular prognostic markers in AML has grown considerably. This is particularly important in the case of patients with normal cytogenetics who comprise the largest subgroup of AML patients (approximately 45%) where many new prognostic factors have been identified. These include gene mutations in FLT3 (Fms-like tyrosine kinase 3; generally FLT3-ITD has been associated with significantly worse survival (Sheikhha et al, 2003)), NPM1 (nucleophosmin 1) and CEBPA (CCAAT enhancer-binding protein-α; generally favorable in cases of biallelic mutations) and gene overexpression as BAALC, WT1, EVI1 and MN1 (Foran, 2010).

Identifying alterations in these genes might provide independent prognostic value in predicting the outcome of acute leukemia, as in the case of the NPM1 mutation gene, which is a relatively frequent abnormality in AML patients and is useful in detecting MRD (Falini et al., 2007).

2. Detailed description of molecular markers

Next, we will describe the most common molecular markers in AML.

2.1 Core Binding Factor (CBF)

Leukemias affecting CBF are characterized by rearrangements of genes that code for components of the heterodimeric transcription factor CBF, which plays an essential role in haematopoiesis (Gabert et al., 2006). CBF complex is a heterodimer composed of RUNX1 (also called AML1) and CBFβ and is the target of at least three common transloctions in AML: t(8;21)/RUNX1-RUNX1T1, t(3;21)/RUNX1-EVI1 and inv(16) or t(16;16) resulting in CBFβ-MYH11. Rearrangements of *AML1* and *CBFB* with other genes lead to chimeric proteins that disrupt the CBF complex, suppressing the activation of transcription.

2.1.1 AML1 (RUNX1) rearrangements

AML1, also called, RUNX1, is normally expressed in all hematopoietic lineages and regulates the expression of several genes specifically linked to hematopoiesis, including the granulocyte colony-stimulating factor receptor, interleukin 3, T-cell receptor, and myeloperoxidase (MPO) genes. The *AML1* gene (on 21q22) is one of the genes most frequently deregulated in leukemias, generally through translocations that produce chimeric messenger RNA. Chimeric protein AML1-ETO (*RUNX1-RUNX1T1)* results from the t(8;21)(q22;q22) involving the AMLI gene on chromosome 21 and the ETO gene on chromosome 8. This rearrangement is detected in approximately 8% of AML cases in children and young adults. *RUNX1-RUNX1T1* is a marker for favourable outcome and an important PCR target for MRD detection. Most patients achieve a CR after induction therapy and those patients benefit most from a postremission therapy with high-dose cytarabin (Bloomfield et al., 1998; Perea et al., 2006). Hence, this marker permits to single out a relatively small subgroup of patients who are more likely to relapse (Gabert et al., 2003). *RUNX1-RUNX1T1* is also frequently associated with c-kit mutations which determine an adverse outcome within this group of patients with favorable prognosis. In addition, the loss of Y chromosome in male patients with t(8;21) leukemia is a negative prognostic factor for the overall survival (Schlenk et al., 2004). While the molecular diagnosis is performed by qualitative and quantitative Real Time RT-PCR (QRT-PCR), MRD monitoring is performed

by quantitative QRT-PCR. The rare balanced t(3;21)(q26;q22) was described in AML, mainly after treatment with topoisomerase II inhibitors. This translocation fuses the AML1 gene on 21q22 and the EVI-1 gene on 3q26 resulting in t(3;21)(q26;q22). This translocation is associated with higher WBC and platelets counts but is not, however, predictive for relapse-free or overall survival (Preudhomme et al., 2000; Meyers et al., 1993; Lutghart et al., 2010).

2.1.2 AML1 mutations

AML1 mutations can be found in *de novo* leukemia, particularly subtypes FAB M0 and M7, as well as in patients with trisomy 21 and myelodysplastic syndromes. Testing for mutations can be performed By real time PCR or PCR-single stranded conformational polymorphism (SSCP). A multivariate analysis carried out by Schnittger et al., showed an independent unfavourable prognostic significance of AML1 (or RUNX1) mutations for overall survival (Schnittger et al., 2011).

2.1.3 CBFb-MYH11

Inv(16)(p13;q22) or t(16;16)(p13;q22) are among the most frequent recurring chromosomal rearrangements detected in AML, generally observed in cases showing myelomonocytic differentiation and having abnormal bone marrow eosinophils (M4 Eo AML in the French American British (FAB) classification). Inv(16)(p13;q22) is found in approximately 10-12% of cases of AML. It can occur in all age groups but is predominantly seen in younger patients. This rearrangement results in the disruption of the myosin heavy chain (MYH) gene at 16p13 and the core binding factor β(CBFβ) gene at 16q22 (FAB, 1976). Ten different CBFβ-MYH11 transcripts have been reported, but the frequency of each transcript is variable. CBFB-MYH11 positive patients are considered to have a favourable prognosis. This rearrangement is frequently associated with c-kit and FLT3 mutations which worsen the prognosis. Quantitative QRT-PCR allows monitoring of CR (Gabert et al., 2003; Perea et al., 2005).

2.1.4 CEBPA

The CCAAT/enhancer binding alpha protein (C/EBPα) is the founding member of a family of related leucine zipper transcription factors. Mutations in CEBPA are found in 5-14% of AML and have been associated with a relatively favourable outcome only in biallelic mutations of this gene. There are two main classes of mutation situated at the N- terminal or

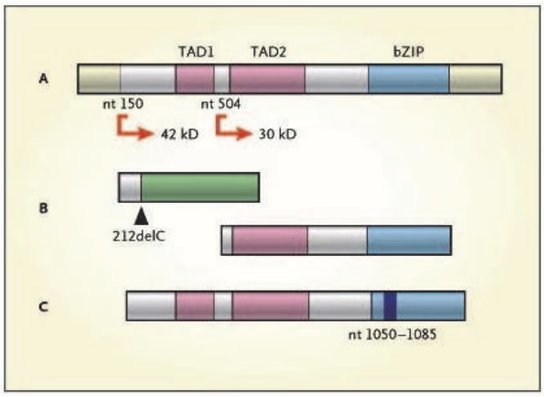

Fig. 1. Schematic representation of CEBPA (by Smith, 2004).

C-terminal basic leucine zipper (bZIP) regions (Figure 1). The latter affect both DNA binding and homo and heterodimerization with other CEBP-proteins. The former introduce a premature stoppage of the translation of the p42 CEBPA protein, preserving a p30 isoform, which was shown to inhibit DNA binding and transactivation by C/EBPα p42. CEBPA mutations are exclusively related to the intermediate risk group karyotype AML. CEBPA insertion, deletions and point mutations are detected usually by DNA sequencing (Wouters et al., 2009; Pabst et al., 2001; Fuchs et al., 2008).

2.2 PML-RARα

Acute promyelocytic leukemia is a distinct subtype of AML (AML-M3) according to the FAB classification. AML-M3 is characterized by t(15;17) that involves the retinoic acid receptor a (RARα) gene on chromosome 17 and the promyelocytic leukemia gene (PML) on chromosome 15. At the molecular level, t(15;17) results in a hybrid PML/ RARα gene, which is easily identified by reverse transcriptase-polymerase chain reaction (RT-PCR). This test provides a rapid and refined diagnosis. The usefulness of minimal residual disease monitoring during follow up (Lo Coco et al., 1992; Lo Coco et al., 1999a) has been well established. The different breakpoints within the PML gene cluster can be located in three regions: bcr1, 2 and 3.

The assessment of remission status at the molecular level by RT-PCR of PML-RARα represents a significant clinical advance with respect to other poorly sensitive methods (morphology, karyotype). The treatment of this disease (arsenicals, liposomal ATRA, other retinoid derivatives, etc) needs to be assessed taking into account the response at the RT-PCR level. The detection of residual PML-RARα transcripts during clinical remission predicts subsequent hematologic relapse. This determines the need for additional treatment given the benefits of anticipating salvage therapy in AML-M3. Figure 3 shows the statistically significant difference between patients treated for molecular relapse and the historical series treated for hematologic relapse (Lo Coco et al., 1999b).

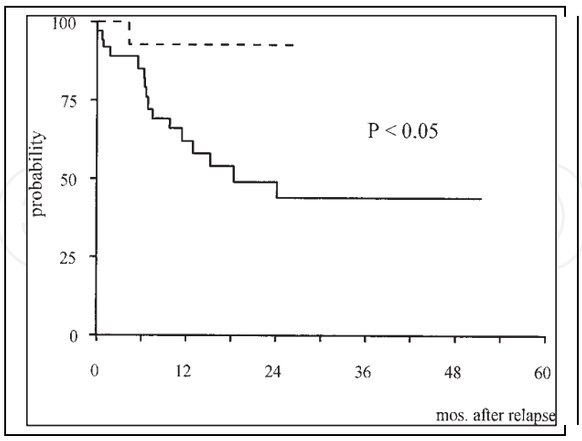

Fig. 2. Kaplan-Meier estimates of overall survival from relapse in patients treated at the time of molecular relapse (dotted line) and in the historical series of patients treated for hematologic relapse (continuous line).

Around 40% of all cases of PML-RARα-positive AML show FLT3 mutations. FLT3-ITD mutations, but not *FLT3-D835*, are associated with characteristic diagnostic hematological

features of acute promyelocytic leukemia, in particular with high WBC counts. Also, FLT3 mutations, especially ITD, can adversely affect overall survival and disease-free survival in PML-RARα-positive AML (Beitinjaneh et al., 2010). However, in a large series of 739 patients with acute promyelocytic leukemia treated with ATRA and anthracycline-based chemotherapy, we were unable to demonstrate an independent prognostic value of *FLT3* mutations (Barragan et al., 2011).

2.3 DEK-CAN

AML defined by t(6;9) is a relatively rare disease, associated with specific clinical and morphological features (Garcon et al., 2005). Especially in young adults, the leukemic phase can be preceded by dysplastic features, conferring a bad prognosis. Morphological findings usually correlate with FAB M2 (60%), M4 (30%), or Ml (von Lindern et al., 1990). A chimeric protein is generated, resulting from the fusion between DEK and the 30- terminus of the CAN gene, also known as NUP214 (von Lindern et al., 1990). DEK is a component of metazoan chromatin capable of modifying the structure of DNA by introducing supercoils. CAN is a nuclear pore complex protein implicated in nucleocytoplasmic trafficking. The CAN gene is also involved in several fusion transcripts described in acute leukemia other than DEK in t(6;9)(p23;q34) AML, such as the SET gene and recently with ABL in T-cell acute lymphoblastic leukaemia (ALL). The DEK-CAN transcript can be used as a marker of t(6;9) AML which can be sensitively monitored by the polymerase chain reaction. This offers a great advantage in the diagnosis, monitoring of response to chemotherapy, and detection of minimal residual disease after bone marrow transplantation (von Lindern et al., 1992). DEK-CAN is related with an adverse prognosis (Dohner et al., 2010).

2.4 NPM1

NPM1 gene is located in 5q35 and encodes a phosphoprotein, nucleophosmin, which moves between the nucleus and the cytoplasm. The gene product is thought to be involved in several processes including regulation of the ARF/p53 pathway. Mutations in exon 12 in this gene are associated with AML with normal karyotype (50%) and especially correlate with monocytic leukemias. Patients with *NPM1* mutations have a significantly higher rate of complete remissions (CRs) after standard induction chemotherapy except for cases associated with internal tandem duplications mutations of FLT3 (Falini et al., 2007; Gale et al., 2008). Gale et al. (2008) identified 3 prognostic groups among the NPM1+ AML patients: good in those with only a NPM1 mutation and absence of a FLT3-ITD; intermediate in those with either absence of FLT3-ITD or NPM1 mutations or mutations in both genes; and poor in those with only FLT3-ITD. Monitoring can be performed by quantitative PCR (Schnittger et al., 2009). In our group, the incidence of NPM1 mutation was 30% (17 of 55 patients with AML), being this prevalence similar to that found for FLT3-ITD in the same population (29 %). The 17 NPM1+ AML patients were distributed as follows: eight M1-M2 (47.1 %), four M4-M5 (23.5%), and five not labelled (29.4 %) because cytogenetic studies were not informative due to several reasons. 64.7% of the NPM1+ patients had a normal karyotype, while 5.8% of them had cytogenetic anomalies. FLT3-ITD mutations were found in 41.2 % of the NPM1+ AML cases. In contrast to what has been described in the literature our group did not find a higher incidence of M4 or M5 subtypes (Thiede et al., 2002). In our case, a higher incidence of M1 and M2 subtypes was detected (Table 4). However the differences are most likely attributable to the small sample size of our cohort as compared to the Thiede

cohort. The global mortality was analyzed disregarding risk factors, with a mortality of 67 % in the NPM1+/FLT3-ITD- group standing in clear contrast to a 100% death rate in the NPM1+/FLT3-ITD+ group (Lopez Jorge et al., 2006). This was confirmed in another study where we analysed the incidence and prognostic relevance of CD34/CD7/DR surface markers in a group of forty two NPM1positive patients and related it to FLT3-ITD mutations. We found that 84% of the NPM1 positive patients had normal karyotypes. Mutations in FLT3-ITD were detected in 23.8% of the NPM1+ patients. The screening for this mutation could be very useful in the future as patients with normal karyotype and expression of this molecular marker is included in a better prognostic subgroup (Gomez Casares et al., 2009; Dohner et al., 2010).

	Nº patients	**NPM1+**	**NPM1-**
Patients (%)	55	17 (30.9)	38(69)
Median (range age) (years)	60 (18-95)	58 (18-82)	60 (19-95)
Age, r**FAB subtype**			
M0	5	0	5
M1/M2	8/10	4/4	4/6
M4/M5	12/4	3/1	9/3
M6	1	0	1
Not labeled	15	5	10
Cytogenetic:			
Normal karyotype	24	11	13
del(5)	2	0	2
del(7)	5	0	5
trisomy 8	1	1	0
t(4;11)	1	0	1
t(8;21)	2	0	2
t(10;11)	1	0	1
t(9;11)	1	0	1
t(12;13)	1	0	1
t(3;10)	1	0	1
+11	2	0	2
-Y	2	0	2
Complex: >3 abnormalities	2	0	2
Non determinated	14	5	9
FLT3-ITD+ (%)	16 (29)	7(41.2)	9(23.6)

Table 4. Cytogenetics and demographic characteristics in a group of 55 AML patients (Lopez Jorge et al., 2006).

2.5 c-KIT

KIT is a proto-oncogene located on chromosome band 4q11-12 and encodes a 145-kDa transmembrane glycoprotein member of the type III receptor tyrosine kinase family. Ligand independent activation of KIT results from mutations in the extracellular portion of the receptor (exon 8), transmembrane and juxtamembrane domains (exons 10 and 11, respectively), and activation loop of the tyrosine kinase domain (exon 17). *c-KIT* mutations have been found in a variable but relatively high frequency (up to 50%) in patients with CBF

AML, including both t(8;21) and the other major type of CBF AML inv(16)(p13q22) or t(16;16)(p13;q22). This appears to confer a quite unfavourable prognosis with higher relapse risk (associated to inv(16) or t(8;21)). An adverse effect on OS in AML with inv(16) has been described, particularly those that occur in exon 17 (Paschka et al., 2006). Such patients may warrant more aggressive or alternative therapy. The presence of the *c-KIT* mutation would be also important because it provides a target for novel tyrosine kinase inhibitor (TKI) therapy (Pollard et al., *2010).*

2.6 FLT3

Flt3 is a member of the class III tyrosine kinase receptor family that includes the c-kit, c-fms, and PDGF receptors. The Flt3 receptor is preferentially expressed on hematopoietic stem cells and mediates stem cell differentiation and proliferation. Interaction of the Flt3 receptor with Flt3 ligand causes receptor dimerization, leading to the activation of the receptor tyrosine kinase and receptor autophosphorylation. The phosphorylated Flt3 transduces activation signals through associations with various cytoplasmic proteins, including ras GTPase-activating protein, phospholipase C, and Src family tyrosine kinases. Activation of the Flt3 receptor by ligand-dependent phosphorylation induces cellular proliferation via activation of cytoplasmic mediators. Thus, constitutive activation of the Flt3 pathway may lead to disease proliferation and may block cellular apoptotic response to conventional chemotherapy. An internal tandem duplication of the juxtamembrane (JM) domain-coding sequence of the *FLT3 (FLT3-IT)* gene on chromosome 13 has been identified in a group of patients with AML. Constitutive activation of the Flt3 receptor tyrosine kinase, either by internal tandem duplication (ITD) mutations of the juxtamembrane domain or point mutations clustering in the second tyrosine kinase domain (TKD mutations as D835), has been found in 20% to 30% of patients with AML and in 30% to 45% of patients with normal karyotype (reviewed by Stirewalt and Radich (2003)). ITD mutations have been associated with an increased risk of treatment failure after conventional chemotherapy (overall survival and disease-free survival were worse for ITD positive patients versus *FLT3* wildtype patients), whereas the prognostic relevance of *FLT3* point mutations is less evident (D835 mutants did not appear to have a worse median overal suvival or disease-free survival compared with the wildtype group) (Sheikhha et al., 2003). Recently, Spassov et al analyzed for *WT1* and *FLT3*-internal tandem duplication (*FLT3-ITD*) expression in 30 samples of AML patients and determined that high *WT1* expression correlated with the presence of *FLT3-ITD* (P = 0·014) and with a lower rate of complete remissions (P = 0·023) (Spassov et al., 2011). The detection of both molecular markers (*WT1* and *FLT3-ITD*) may be helpful in defining high risk AML patients that need special therapeutic strategies.

Several studies described that a higher mutational load as determined by calculation of *FLT3-ITD/FLT3* wildtype ratio indicates a worse prognosis in mutation carriers. Therefore, it was suggested that not the FLT3-ITD per se, but more likely loss of heterozygosity is associated with the unfavorable outcome in FLT3-ITD mutated AML (Meshinchi et al., 2001; Yanada et al., 2005; Thiede et al., 2002; Schnittger et al., 2011).

2.7 EVI1 overexpression

The ectopic viral integration site 1 (EVI1), located in chromosome 3q26, has been recognized in the last years as one of the most aggressive oncogenes associated to human leukemia (Gröschel et al., 2010). The inappropriate expression of EVI1 in hematopoietic cells has been

implicated in the development or progress of myeloid disorders (Lugthart et al., 2008). Previous studies, applying microarray technology, indicate that high levels of EVI1 expression are detected in 10% -22% of patients with AML (Barjesteh et al., 2003). Although the higher expression of EVI1 gene was clearly associated with myeloid malignancies, is not restricted to this group. It is noteworthy that overexpression of EVI1 was also observed in 13.8% of patients with acute lymphoid leukemia. The correlation between overexpression of EVI1 in bone marrow and poor outcome in AML is a frequent issue of discussion in the literature (Lugthart et al., 2008; Luzardo et al., 2007).

We analyzed the incidence of EVI1 overexpression in haematological malignancies and its value as a prognostic factor. EVI1 overexpression (EVI1+) was examined by RT-PCR in bone marrow and/or peripheral blood samples of 113 AML patients at diagnosis and during follow-up. We found that 23.8% of AML overexpressed EVI1, as established by our previously determined cut-off point. Correlation with FAB subtypes stands as follows: 2M0, 1 M1,3 M2, 6 M4, 7 M5, 1 M6, 4 secondary AML and 3 not labeled. Survival curves in the AML group didn´t show any significant differences in overall survival and disease free survival when comparing EVI1+ to EVI1- populations. In AML samples a greater than expected incidence of EVI1 expression was observed (22.8% vs 11% previously described). When survival curves were analyzed in the AML group with ages ranging from 14 to 60 years, all of them treated with similar chemotherapy schemes, no significant difference was observed. However, a recent collaboration with other groups, showed that *EVI1* overexpression is a poor prognostic marker in patients <65 years in an independent large cohort, and showed that the total absence of *EVI1* expression has a prognostic impact in the outcome of acute myeloid leukemia patients (Vazquez et al.,2011).

2.8 BAALC AND MN1

The Brain and Acute Leukemia Cytoplasmic *(BAALC)*, human gene located on chromosome 8q22.3, has also been found to be an important adverse prognostic factor if overexpressed in normal karyotype AML, suggesting a role for BAALC overexpression in acute leukemia. This gene is highly conserved in mammals. Normally, BAALC is almost exclusively expressed in neuroectoderm-derived tissues. Though little is known about the biological function of BAALC, it is highly expressed in hematopoietic precursor cells as well as leukemic blasts and is down-regulated during differentiation. BAALC has been postulated to play its role in the cytoskeleton network due to its cellular location. BAALC expression is an independent adverse prognostic factor and is associated with a specific gene-expression profile. Recent studies revealed the prognostic impact of BAALC expression in AML and also as a marker in minimal residual disease. Currently, determination of BAALC expression is performed by qualitative and quantitative real-time PCR, although the lack of validation or standardization studies limits its utility (Tanner et al., 2001; Gregory et al., 2009; Baldus et al., 2003; Najima et al., 2010).

The meningioma 1 *(MN1)* gene is localized on human chromosome 22. *MN1* overexpression is a prognostic marker in patients with AML with normal karyotype characterized by an intermediate prognosis. Patients with high *MN1* expression had a significantly worse prognosis (the overall survival was shorter and relapse rate was higher in this group compared to low *MN1* expression group). High *MN1* expression has as well been associated with other AML characteristics like inv(16) or overexpression of *EVI-1* (Heuser et al, 2007). In addition, MN1 is able to induce myeloid leukemias in a murine model (Heuser et al, 2011). This suggested that MN1 may play a functional role in the pathogenesis of AML.

We performed a retrospective analysis of MN1 expression in a group of 49 AML patients with a mean age of 52 years (43 de novo AML and 6 secondary AML). In order to analyze response to chemotherapy, overall survival and correlation to other molecular markers (NPM1, FLT3-ITD, EVI1 and BAALC), patients were further classified into three groups depending on prognosis (favourable with 11 patients, intermediate with 25 and poor with 12). We analysed by real-time PCR the expression of MN1 in patients samples. We used as positive control of expression RNA of KG1 cell line that overexpress MN1. The incidence of MN1 overespression was 65.3%. The study showed that MN1 overexpression correlated to BAALC expression. We did not find relation with other markers, such as EVI-1, NPM-1 and FLT3. MN1 and BAALC overexpression have been associated to induction treatment refractoriness. However, due to the limited sample size in our series, determining whether MN1 or BAALC were actually involved with refractoriness was not possible. The 2-year overall survival was 52% and 53% for MN1 overexpressed and MN1 not overexpressed patients respectively. The 5-year overall survival was 52% and 42% respectively, showing no significant differences. Survival analysis for the intermediate risk AML group did not show significant differences either. MN1 overexpression was not associated with a worse prognosis in any of the studied patients, probably due to a small sample size (Rodriguez et al., 2010).

2.9 WT1

The Wilms' tumor locus was identified as a tumor suppressor gene, which is inactivated in Wilms' tumor, a pediatric kidney cancer. This protein, displaying characteristic features of a transcription factor, and with an expression restricted to kidney and haematopoetic cells, was called Wilms' tumor gene 1 (*WT1*). This gene is located on chromosome 11p13 and encodes a zinc-finger transcription factor influencing the expression of several growth factors and their corresponding receptors. It is also known to be involved in the early stage of hematological cell differentiation. Aberrant expression may be one mechanism by which the normal function of *WT1* is disrupted. However, the exact role of *WT1* in hematopoiesis and leukemogenesis still remains unclear. The abundant overexpression of *WT1* in leukemia creates a very attractive target for quantitative MRD studies in AML, especially in those samples with no specific fusion gene available. The method used to determine the expression of *WT1* gene is the RT-PCR, which will reveal its value as a marker to detect minimal residual disease (Keilholz et al., 2005; Weisser et al., 2005; Inoue et al., 1994; Garg et al., 2003).

Mutations of the coding region (most frequenly in 7 and 9 exons) of the *WT1* gene have also been described and occur in 10–15% of AML (figure 3). Gaidzik et al. concluded that *WT1* mutation as a single molecular marker did not have an impact on outcome. On the other hand, Hou et al. demostrated that *WT1* mutations disappeared in *WT1*-mutated studied patients who achieved complete remission, suggesting its potential use as MRD marker (Gaidzik et al., 2009; Hou et al., 2010).

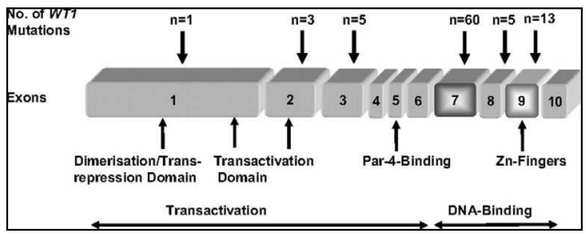

Fig. 3. Structure of the *WT1* gene and localization of the 87 mutations identified by Gaidzik et al.

2.10 MLL rearrangement and MLL-PTD

The *MLL* (mixed lineage leukemia) gene located at 11q23, is fused to a variety of partner genes through chromosomal translocations in acute leukemias. Up to now, more than 40 different *MLL* partner genes have been identified. *MLL* gene contains 100 kb of DNA, but nearly all breakpoints are clustered within a 8.3 kb region. Molecular analysis shows that fusion of the amino terminus of *MLL* to the carboxy terminus of partner genes generates the critical leukemogenic fusion proteins. Abnormalities of the mixed-lineage leukemia (*MLL*) gene can be detected in *de novo* acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) as well as in therapy-related AML, particularly after treatment with DNA topoisomerase II inhibitors (generally less than 5–10% of patients carried this rearrangements).The most common translocation involving 11q23 in acute myeloid leukemia (AML) is t(9;11)(p22;q23), which results in the generation of a fusion transcript of *MLL-AF*. The other common translocations involving 11q23 in AML are t(6;11)(q27;q23), t(10;11)(p12;q23), t(11;19)(q23;p13.1) and t(11;19)(q23;p13.3); these translocations result in the generation of fusion transcripts *MLL-AF6*, *MLL-AF10*, *MLL-ELL* or *MLL-ENL*, respectively. In AML, *MLL-AF9* has generally been associated with a more favourable outcome although this finding is controversial. This rearrangement is related to a superior event-free and overall survival as compared to patients with other chromosomal abnormalities or with no detectable rearrangements (Dimartino et al., 1999; Balgobind et al., 2005). In contrast, the other traslocation involving Cr 11q23 are asociated with poor prognostic in more cases (Dimartino et al., 1999; Balgobind et al., 2005). t(9;11)(p22;q23) is classified as intermediate and t(v;11)(v;q23) as adverse prognostic group (Döhner et al., 2010). Therefore, detection and identification of the different types of *MLL* rearrangements is of clinical importance. A recent study indicated that quantification by RQ-PCR of the fusion gene transcript levels at diagnosis may be of prognostic relevance (Shih et al., 2006; Jansen et al., 2005). One type of *MLL* rearrangement not detectable by classic cytogenetic is the partial tandem duplication of *MLL* (*MLL*-PTD). This rearrangement results most commonly from a duplication of a genomic region encompassing either *MLL* exons 5 through 11 or *MLL* exons 5 through 12 that is inserted into intron 4 of a full-length *MLL* gene, thus fusing introns 11 or 12 with intron 4. At a transcriptional level, this results in a unique in-frame fusion of exons 11 or 12 upstream of exon 5. In adult de novo AML with a normal karyotype, the presence of the *MLL*-PTD has been associated with a worse prognosis (ie, shorter duration of remission) when compared with normal karyotype AML without the *MLL*-PTD (Whitman et al., 2005).

2.11 Other molecular markers in research: Renin expression

There have been reports of experimental findings that relate the renin-angiotensin system (RAS) with hematopoiesis. Some studies have identified RAS components located in the bone marrow (Haznedaroglu & Buyukasik, 1997) that might functionally affect cellular proliferation and differentiation in physiological or pathological states (Huckle & Earp, 1994; Comte et al., 1997). It has been demonstrated that the RAS component renin is expressed in the bone marrow microenvironment as well as in hematopoietic cells (Abali et al., 2002). Bone marrow blast cells of some types of AML (M4 and M5 FAB types) express renin (Wulf et al., 1998), however no expression has been detected in normal bone marrow from healthy donors (Gómez Casares et al., 2002). Our group also detected renin expression

in AML patients, but it did not relate to monocytic dififerentiation or to the existence of other cytogenetic risk markers (Gómez Casares et al., 2002). Moreover, renin expression has been found to be related to disease activity, disappearing with AML remission and returning with relapse (De la Iglesia et al., 2006).
We did not found statistically significant differences in the outcome between renin-positive and renin-negative patients (De la Iglesia et al., 2006).

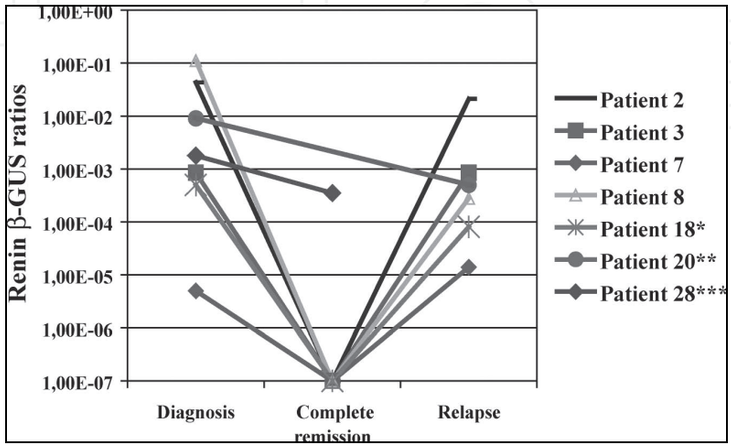

Fig. 4. Renin:βglucuronidase ratios vs clinical state of the quantified patients. *This data belong to third relapse, CR and fourth relapse, respectively. **This patient did not reach CR, continuing the positivity of the renin gene expression. ***Patient 28 in morphological CR was presented with 1% blasts in BM that later disappeared (De la Iglesia et al., 2006).

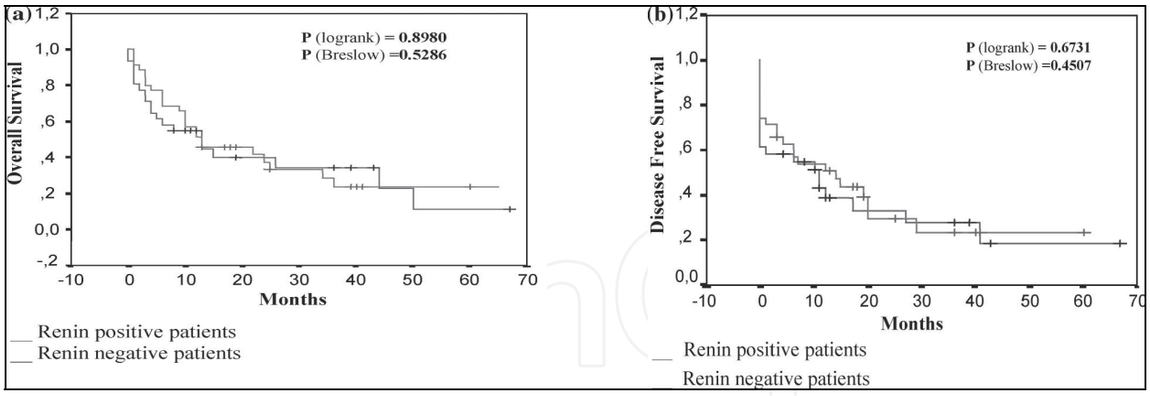

Fig. 5. (a) Overall survival of renin-positive and renin-negative patients with AML. Kaplan-Meier plot showing the correlation between overall survival and renin expression in AML patients. (b)Disease-free survival of renin-positive and renin-negative patients with AML. Kaplan-Meier plot showing the correlation between disease-free survival and renin expression in AML patients. (De la Iglesia et al., 2006).

Renin expression is related to undifferentiated phenotypic cell lines (K562, KU812), since no expression of the renin gene was found in cellular lines that showed a highly differentiated phenotype like HL60 and U937 (Gómez Casares et al., 2002). ACE inhibitors (captopril and trandolapril) and AT1 receptor blocker (losartan) produce a stop in

proliferation in K562 cells with captopril (C) 10 mM and trandolapril (T) 2 mM (figure 6a) as well as an increase in the apoptotic rate in renin positive leukemia cell lines (K562) after the treatment with captopril (data not shown) and trandolapril (figure 6b) (De la Iglesia et al., 2009).

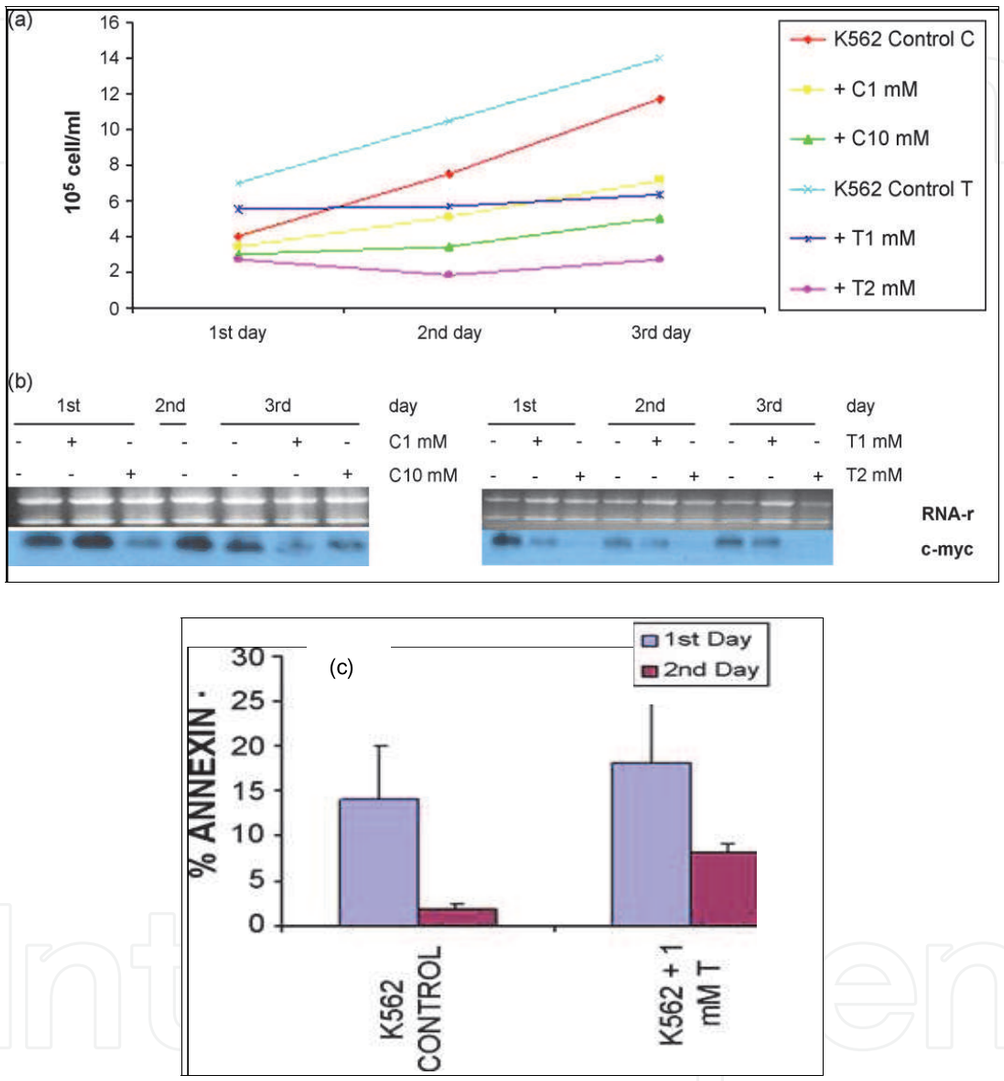

Fig. 6. **(a)** Proliferation in K562 after the treatment with captopril (C) and trandolapril (T). **(b)** C-myc gene expression in K562 after the treatment with the same drugs. **(c)** Apoptosis determined by annexin V binding in K562 and K562 transfected with bcl-2 and bcl-x (Kbcl2 and Kbclx) cells treated with 1mM trandolapril (T) (De la Iglesia et al., 2009). All experiments were performed in triplicate.

The leukaemogenic role of renin gene expression and the implicated molecular pathways have not yet been elucidated but it may offer novel therapeutic approaches in pathological or neoplastic conditions (Haznedaroglu & Öztürk, 2003).

3. Conclusion

The AML embraces very heterogeneous entities with different clinical behaviours. Some of these leukemias have certain chromosomal alterations that are related to specific morphological and clinical subtypes. Their identification has had great impact on different management aspects of these diseases, either from the standpoint of diagnosis, prognosis or development of a treatment plan tailored to the risk of relapse. This has been largely possible thanks to the application of molecular biology studies, which have provided a better and deeper understanding of the pathogenesis of leukemia.

The genetic alterations that occur at different stages fall into two broad groups: those that activate signal transduction as c-KIT and FLT3 (type I) and those which alter transcription factors such as CBF, RAR-α, CEBPA and NPM1 (type II). These two groups work together in leukemogenesis, being very frequent the coexistence of alterations of the two groups in the same patient.

The knowledge of these molecular markers helps us to classify patients within certain prognostic groups. In this way, in patients with normal cytogenetics, it is very important to know if there is a mutation of the FLT3 gene as well as its kind (ITD or TKD), because this information is of great relevance in order to select the appropriate treatment scheme. Moreover, the overexpression of the genes BAALC (under OS, DFS), MN1 (induction failure in patients with normal karyotype) or EVI1 (adverse impact) has been shown to have prognostic significance in AML.

In a laboratory setting there are different ways to classify leukemias. One of them is the rationale showed in the figure 5. According to the cytogenetic or molecular biology at diagnosis, it is possible to perform different determinations which will allow us to classify the patients within a favourable or unfavourable prognostic group. AML patients are classified at the time of diagnosis into three different prognostic groups based on their cytogenetic profiles.

There are plenty of algorithms which allow us to classify patients into different prognostic groups. They are undergoing continuous changes with the enrichment of new data. If we are in the presence of a CBF leukemia (by showing RUNX1-RUNXT1 or inv (16)), mutational analysis of c-kit should be performed, as this mutation translates into a higher risk of relapse. In patients with AML with normal karyotype, we recommend to analyze for FLT3-ITD first, as FLT-ITD3 is a well-known adverse prognostic factor. We then recommend screening for NPM1 mutations as a next step, because it is another mutation with clinical relevance of this subgroup of patients in the absence of FLT3-ITD. Then, given the favourable prognosis of NK-AML with biallelic CEBPA mutation, we recommend a CEBPA mutational analysis in those patients non-carriers of FLT3-ITD or NPM1. Also, FLT3-TKD an others mutations can be analyze in a context of clinical trials, even though there is no prognostic relevance.

There after, it is possible to perform other studies such as the detection of mutations in MLL/AF9 or BAALC, MN1 and EVI1 gene overexpression in order to make a better stratification of the prognosis. Besides working with prognostic and follow up markers with a recognized utility, we are also carrying out experimental work with new, not yet validated markers which will probably help us in the follow up, prognosis, classification and monitoring of AML patients. Renin, EVI1 and WT1 would be markers applicable to AML patients, especially in those with normal karyotype where they will facilitate the monitoring of minimal residual disease.

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

Table 5. Standardized reporting for correlation of cytogenetic and molecular genetic data in AML with clinical data (Döhner. European LeukemiaNet , 2010)

In recent past, treatments had an empirical basis, lack of specificity and, therefore, limited effectiveness combined with high toxicity. The treatment of AML pioneered the search for specific therapies with the use of ATRA in APL. Currently, the ultimate goal of the understanding and classification of molecular aberrations in every AML subtype is to design a targeted therapy, which will reduce the risk of relapse and treatment side effects. That is because the future of AML therapy should be in the search and development of drugs that are directed against specific molecular or fusion proteins aberrations. On the other hand, due to the interaction between different molecular aberrations that arise in AML, the design of these new drugs has to be focused on the combined inhibition of several signalling pathways to achieve maximum clinical benefit.

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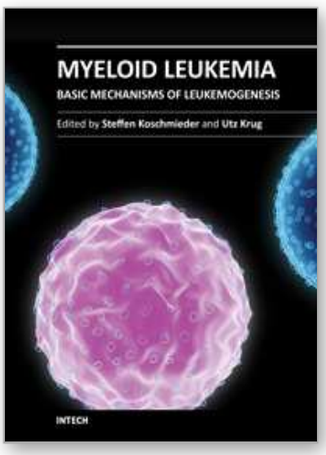

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The current book comprises a series of chapters from experts in the field of myeloid cell biology and myeloid leukemia pathogenesis. It is meant to provide reviews about current knowledge in the area of basic science of acute (AML) and chronic myeloid leukemia (CML) as well as original publications covering specific aspects of these important diseases. Covering the specifics of leukemia biology and pathogenesis by authors from different parts of the World, including America, Europe, Africa, and Asia, this book provides a colorful view on research activities in this field around the globe.

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