Current Research in Translational Medicine 71 (2023) 103421

Contents lists available at ScienceDirect

Current Research in Translational Medicine

journal homepage: www.elsevier.com/locate/retram

Cytogenetics in the management of acute myeloid leukemia and histiocytic/dendritic cell neoplasms: Guidelines from the Groupe Francophone de Cytogénétique Hématologique (GFCH)

ARTICLE INFO

Keywords
Acute myeloid leukemia
Histiocytic/dendritic cell neoplasms
Cytogenetic abnormalities
Prognosis

ABSTRACT

Genetic data are becoming increasingly essential in the management of hematological neoplasms as shown by two classifications published in 2022: the 5th edition of the World Health Organization Classification of Hematolymphoid Tumours and the International Consensus Classification of Myeloid Neoplasms and Acute Leukemias. Genetic data are particularly important for acute myeloid leukemias (AMLs) because their boundaries with myelodysplastic neoplasms seem to be gradually blurring. The first objective of this review is to present the latest updates on the most common cytogenetic abnormalities in AMLs while highlighting the pitfalls and difficulties that can be encountered in the event of cryptic or difficult-to-detect karyotype abnormalities. The second objective is to enhance the role of cytogenetics among all the new technologies available in 2023 for the diagnosis and management of AML.

Introduction

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults and has a low overall survival (OS) rate (5-year survival rate = 24%). The incidence rate of AML is approximately 4 cases per 100,000 adults and 0,7 cases per 100,000 children annually [1–3]. The incidence increases with age, with a median age at diagnosis of 68 years [1]; thus, the aging of the population leads us to anticipate an increase in the incidence of AMLs in the coming years.

AML is a heterogeneous group of hematological neoplasias characterised by malignant clonal expansion of myeloid-committed progenitor cells coupled with differentiation arrest. Since the first description of translocation in AML [4], advances in genomic techniques have improved our understanding of the processes of leukemogenesis in relation to cytogenetic and/or molecular abnormalities. Currently, it is estimated that approximately 50% of adult patients and 75% of pediatric patients have chromosomal abnormalities (CAs) and that > 95% of patients have at least one mutation. Given the importance of genetic abnormalities in the development of AML, their detection is critical for diagnosis and prognosis.

In 2022, two major classifications including AML were published: the 5th edition of the World Health Organization Classification of Hematolymphoid Tumours (WHO-HAEM5) [5] and the International Consensus Classification of Myeloid Neoplasms and Acute Leukemias (ICC-2022) [6]. Although quite similar, these two classifications have some differences (Table 1) that sometimes make it difficult to reach a consensus on the diagnosis and interpretation of genetic results.

Regarding the prognosis, the distribution of CAs in AML is age-related: recurrent balanced translocations with a favourable prognosis are more frequent in children and young adults, whereas abnormalities with an intermediate or unfavourable prognosis are more frequent in adults aged >60 years [2]. The 2022 European LeukemiaNet (ELN-2022) recommendations [2] are among the most widely used prognostic classifications. Blastic plasmacytoid dendritic cell (pDC) neoplasm (BPDCN) has been introduced into the 'Histiocytic and dendritic cell neoplasms' chapter of the current WHO-HAEM5 and contains a new subgroup referred to as mature pDC proliferation (MPDCP) associated with myeloid neoplasms [5].

We herein present the most relevant CAs in terms of diagnosis and/or prognosis in AML and pDC disorders, as listed in Table 2. We conclude by focusing on new cytogenomic techniques, such as those based on next generation sequencing (NGS) and optical genome mapping (OGM), which could become the gold standard of testing and replace chromosomal banding analysis (CBA) and FISH in the near future.

1. Cytogenetic abnormalities

1.1. AML

1.1.1. AML with recurrent cytogenetic abnormalities

1.1.1. 1. t(15;17)(q24;q21)/PML::RARA and other 17q21/RARA-r AMLs. The recurrent translocation t(15;17)(q24;q21), observed in M3/M3v forms of the French-American-British (FAB) classification and leading to *PML::RARA* fusion, is specific for acute promyelocytic leukemia (APL) [5,6]. This translocation is found in 80–90% of patients with APL [7,8] and leads to the expression of a functional PML::RARA chimeric protein. APL with *PML::RARA* fusion accounts for 5–10% of adult and pediatric AMLs. The clinical presentation may be aggressive and complicated by a life-threatening coagulation disorder. Diagnosis

https://doi.org/10.1016/j.retram.2023.103421
Received 4 July 2023; Received in revised form 29 September 2023; Accepted 15 October 2023
Available online 16 October 2023

Table 1
Comparison of cytogenetic abnormalities in WHO-HAEM5 and ICC-2022

WHO-HAEM5 [4]	ICC-2022 [5]
AML with defining genetic abnormalities	**AML with recurrent genetic abnormalities**
elimination of the 20% blasts requirement (except for *BCR::ABL1 and CEBPA*)	**requiring ≥ 10% blasts in BM or PB (except for *BCR::ABL1*)**
APL with *PML::RARA* fusion	APL with t(15;17)(q24;q21.2)/*PML::RARA*
APL with a variant *RARA* translocation	APL with other *RARA* rearrangements[a]
AML with *RUNX1::RUNX1T1* fusion	AML with t(8;21)(q22;q22.1)/ *RUNX1::RUNX1T1*
AML with *CBFB::MYH11* fusion	AML with inv(16)(p13.1q22) or t(16;16)(p13,1;q22)/*CBFB::MYH11*
AML with *KMT2A* rearrangement	AML with t(9;11)(p21.3;q23.3)/*KMT2A::MLLT3*
	AML with other *KMT2A* rearrangements[b]
AML with *DEK::NUP214* fusion	AML with t(6;9)(p22.3;q34.1)/*DEK::NUP214*
AML with *MECOM* rearrangement	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM (EVI1)*
	AML with other *MECOM* rearrangements[c]
AML with *BCR::ABL1* fusion	AML with t(9;22)(q34.1;q11)/*BCR::ABL1*
AML with *NPM1* mutation	
AML with *CEBPA* in-frame bZIP mutation	
	AML with other rare recurring translocations
AML with *RBM15::MRTFA* fusion	t(1;22)(p13.3;q13.1)/*RBM15::MRTFA*
AML with *NUP98* rearrangement	t(5;11)(q35.2;p15.4)/*NUP98::NSD1*
	t(11;12)(p15.4;p13.3)/*NUP98::KMD5A*
	AML with *NUP98* and **others** partners
AML with other defined genetic alterations	t(1;3)(p36.3;q21.3)/*PRDM16::RPN1*
AML with *RUNX1T3*(*CBFA2T3)::GLIS2*	t(3;5)(q25.3;q35.1)/*NPM1::MLF1*
AML with *KAT6A::CREBBP*	t(7;12)(q36.3;p13.2)/*ETV6::MNX1*
AML with *FUS::ERG*	t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP*
AML with *MNX1::ETV6*	t(10;11)(p12.3;q14.2)/*PICALM::MLLT10*
AML with *NPM1::MLF1*	t(16;21)(p11.2;q22.2)/*FUS::ERG*
	t(16;21)(q24.3;q22.1)/*RUNX1::CBFA2T3*
	inv(16)(p13.3q24)/*CBFA2T3::GLIS2*
AML, myelodysplasia-related (AML-MR)	**AML with myelodysplasia-related cytogenetic abnormalities**
AML with ≥20% blasts	**AML if ≥20% blasts; otherwise 10-19% blasts : MDS/AML with myelodysplasia-related cytogenetic abnormalities**
Complex karyotype : ≥3 abnormalities*	
idic(X)(q13)	
del(5q) or loss of 5q due to unbalanced translocation	del(5q)/t(5q)/add(5q)
-7/del(7q) or loss of 7q due to unbalanced translocation	-7/del(7q)
del(12p) or loss of 12p due to unbalanced translocation	del(12p)/t(12p)/add(12p)
i(17q)/del(17p) or loss of 17p due to unbalanced translocation	i(17q)/-17/add(17p) or del(17p)
del(11q)	+8
-13/del(13q)	del(20q)

[a] other recurring translocations involving *RARA* should be reported : APL with t(11;17)(q24.3;q21.2)/*RF2BP2::RARA*; APL with t(5;17)(q35.1;q21.2)/*NPM1::RARA*; APL with t(11;17)(q23.2;q21.2)/*ZBTB16::RARA*; APL with cryptic inv(17) or del(17)(q21.2q21.2)/*STAT5B::RARA*; *STAT3::RARA*; others genes rarely rearranged with *RARA* :*TBL1XR1* (3q26.3); *FIP1L1* (4q12); *BCOR* (Xp11.4)

[b] other recurring translocations involving *KMT2A* : AML with t(4;11)(q21.3;q23.3)/*KMT2A::AFF*; AML with t(6;11)(q27.q23.3)/*KMT2A::AFDN*; AML with t(10;11)(p12.3;q23.3)/*KMT2A::MLLT10*; AML with t(10.11)(q21.3;q23.3)/*KMT2A::TET1*; AML with t(11;19)(q23.3;p13.1)/*KMT2A::ELL*; AML with t(11;19)(q23.3;p13.3)/*KMT2A::MLLT1*

[c] other recurring translocations involving *MECOM* : AML with t(2;3)(p11~23;q26.2)/*MECOM::?;* AML with t(3;8)(q26.2;q24.2)/*MYC::MECOM*; AML with t(3;12)(q26.2;p13.2)/*ETV6::MECOM*; AML with t(3;21)(q26.2;q22.1)/*MECOM::RUNX1*

* in the absence of other class-defining recurring genetic abnormalities

must be rapid with demonstration of t(15;17)(q24;q21) or *PML::RARA* fusion by fluorescence *in situ* hybridisation (FISH) and/or molecular techniques. After the initial critical stage, the use of all-trans retinoic acid (ATRA) in combination with arsenic trioxide (ATO) or chemotherapy allows the achievement of OS and progression-free survival rates that are superior to those of other AMLs.

Besides the classical t(15;17), complex or unbalanced rearrangements or chromosomal insertions of *RARA* into *PML* or *PML* into *RARA* can occur [9]. In a retrospective analysis, Gagnon et al. [7] found that 2.3% of cases had three- or four-partner translocations and 0.7% had cryptic insertions. The use of dual-colour/double-fusion FISH probes with filter-by-filter reading by an experienced cytogeneticist is

Table 2
Cytogenetic abnormalities in acute myeloid leukemia (AML) and Plasmactoid dendritic cell disorders

Cytogenetics Abnormalities	Genes involved (chromosome localisation)	Driver derivative chromosome	Frequency	Prognosis	Main cytological and immunophenotypical features	Main clinical features	Most frequently secondary abnormalities	References
Acute Myeloid Leukemia								
Cytogenetic abnormalities with count blasts <20% acceptable for AML diagnosis								
t(15;17)(q24;q21)	*PML*(15q24):: *RARA*(17q21)	der(15)	5-10%	Good	Promyelocytic	DICV	+8, -7/del(7q), del(9q),+11, +21	[7]
t(8;21)(q22;q22.1)	*RUNX1*(21q22):: *RUNX1T1*(8q22)	der(8)	5 - 15% more frequent in children and young adults, rare in elderly patients	Good	M2 subtype with unique Auer rods and aberrant markers such as CD19 and CD56		-X/-Y, del(9q)	[2,13,16,17]
inv(16)(p13.1q22)	*CBFB*(16q22):: *MYH11*(16p13)	16p	5-10%	Good	Myelomonocytic with abnormal eosinophils (M4eo subtype)		+22,+8,+21, 3'CBFB deletion	
t(16;16)(p13.1;q22)				Good				
11q23 rearrangements	*KMT2A/MLL* (11q23.3)	der(11)	2-5% (A) 15-20% (P) 47-55% (I)	Poor*	Myelomonocytic and monoblastic		+6,+8,+19,+21	[2,25–28]
t(9;11)(p21;q23.3)	*MLLT3*(9p21):: *KMT2A*(11q23)		1-2% (A) 5-12% (P)	Int	Myelomonocytic and monoblastic		none	
ins(10;11)(p12;q23q?)	*KMT2A(11q23):: MLLT10(10p12)*	der(10)	2-3% (P), infants ++	Poor	Monoblastic			
t(6;9)(p23;q34)	*DEK*(6p23):: *NUP214*(9q34)	der(6)	0,9-1,8% mainly children and young adults, no infant cases / may be underestimated	Poor	Dysplasia and basophilia (at least 2% basophils)		Mostly isolated	[8,32–34]
3q26 rearrangements	*MECOM/EVI1* (3q26)	/	2-4%	Poor	Dysplasia	Platelet abnormalities	-7/del(7q)	[2,8,42–44]
11p15 rearrangements**	*NUP98* (11p15)	der(11)	3-5% (P) rare in adults (young adults ++)	Poor			none	[48–50,54]
t(5;11)(q35;p15)	*NUP98*(11p15):: *NSD1*(5q35)		3-4% (P) 2% (A) **/!\ cryptic**	Poor	Myelomonocytic and monoblastic		apparently normal karyotypes	
t(11;12)(p15;p13)	*NUP98*(11p15):: *KDM5A*(12p13)		2% (P) 12%(I)	Poor	AMKL		CK	
t(1;22)(p13;q13)	*RBM15*(1p13):: *MKL1*(22q13)	der(1)	0,3%(P) Infants++	Int	AMKL, frequent myelofibrosis	Hepatosplenomegaly	Mostly isolated, duplication der(1)t(1;22), hyperdiploidy (+2,+6,+19, +21)	[51,56,64,65,71,72]
Other cytogenetic abnormalities (count blasts ≥20% required for AML diagnosis)								
t(9;22)(q34;q11)	*BCR*(22q11):: *ABL1*(9q34)	der(22)	<1%	Poor			-7, +8, CK	[2,8,36,37]
t(8;16)(p11.2;p13.3)	*KAT6A*(8p11):: *CREBBP*(16p13)	both der(8) and der(16)	<1%, the most frequent in neonates	Poor, Int in pediatrics	Myelomonocytic and monoblastic with erythrophagocytosis	t-AML, extra-medullary (cutaneous) and DICV Spontaneous remission in neonates	Del(5q), del(7q), del(9q),+1q,	[45,46]
t(7;12)(q36;p13)	*ETV6*(12p13):: *MNX1*(7q36)	der(12)? pathogenic mechanisms not fully understood	4,3% (I), never observed in adults / may be underestimated	Poor			+19	[58]
inv(16)(p13.3q24.3)	*CBFA2T3*(16q24):: *GLIS2*(16p13)	16q	2-3% (P), infant ++	Poor	Megakaryoblastic (30% of non DS peadiatric AMKL), CD56+ HLA-DR- CD45- CD38-		Low hyperdiploidy, +3, +21, +Y	[51,61–64,66]

(*continued on next page*)

Table 2 (*continued*)

t(16;21)(p11q22)	*FUS*(16p11):: *ERG*(21q22)	der(21)	0,3-0,5% (P)	Poor	possible abnormal or elevated eosinophils or erythrophagocytosis		ACAs frequents, +8, +10	[68]
t(16;21)(q24;q22)	*RUNX1*(21q22):: *CBFA2T3*(16q24)	der(16)	0,1-0,3% (P)	Good	M1 and M2	t-AML	-X/-Y,+8	[68,69]
t(10;11)(p12;q14)	*PICALM* (11q14):: *MLLT10* (10p12)	not known which of the 2 fusion protein has the critical role	<1% (P)	Int	Aberrant marker CD7	Extramedullar disease	+4, +19	[30]
+8	/	/	?(A) 10-14% (P)	Int			Mainly secondary **/!** search for primary abnormality	[5,32]
Monosomy 7[M]	/	/	5% of AML (A) <60y, 3% (P)	Poor	Myelodysplasia related		CK	[2,8,73]
Del(7q)***[M]	/	/	2-3%	Int			CK	
Chromosome 5 abnormalities[M] **(-5, del5q,add5q)**	/	/	5-10% (A) 1% (P)	Poor	Myelodysplasia related		CK	[2,8]
Chromosome 17 abnormalities[M] **(-17, del17p,i(17q))**	Loss of *TP53*	/	5%	Poor			CK	[2,76,79]
idic(X)(q13)[M]	/	/	rare, elderly women ++	Int	Myelodysplasia related		Mostly isolated or duplication of the idic	[85]
Complex karyotypes (CK)[M]	/	/	10-12% (A) 8% (P)	Poor, still discussed in pediatric		Secondary and therapy related AML		[2,8,42,56,57, 81]
Monosomal Karyotype (MK)	/	/	13% (A) 3% (P)	Poor		Secondary and therapy related AML	CK, -7	[2,44,84]
Normal Karyotype	/	/	50% (A) 20-25% (P)	Int				[5,32]
Plasmactoid dendritic cell disorders								
Abnormalities found in Blastic plasmacytoid dendritic cell neoplasm (BPDCN)								
Complex karyotypes (CK)	/	/	90%	no prognostic impact			Monosomies and deletions	[94,95,104]
Del(5q)	*NR3C1* (5q31)	/	72%				Co-occurrence of 3 or more of these six abnormalities in half of the cases	
Del(6q)	*IFNGR1* (6q23), *TNFAIP3* (6q23)	/	50%					
-9	*CDKN2A-B* (9p21)	/	28%					
Del(12p)	*ETV6* (12p13), *CDKN1B* (12p13)	/	64%					
Del(13q)	*RB1* (13q14)	/	64%					
Del(15q)/-15	/	/	43%					
8q24 rearrangements	*MYC* (8q24)	/	8-38%	no prognostic impact	Immunoblastic morphology and CD10+	Elderly patients		[99,100]
t(6;8)(p21;q24)	*RUNX2*(6p21):: *MYC*(8q24)		The most frequent of *MYC* rearrangements					
6q23 rearrangements	*MYB* (6q23)	der(6)	20%	no prognostic impact		Children		[99,102]
t(1;6)(q21;q23)	*MYB*(6q23):: *PLEK01*(1q21)							
t(6;8)(q23;q24)	*MYB*(6q23):: *ZFAT*(8q24)							
Abnormalities found in AML associated with a pDC expansion (pDC-AML)								
Del(7q)		/	13%	Int				[74,106]
+13		/	7%					

(*continued on next page*)

Table 2 (*continued*)

(A): Adults, (P): Pediatric, (I): Infant (<2ans), t-AML: Therapy related AML, Int: intermediate

*Except for adults the t(9;11)(p21,3;q23.3)/*KMT2A::MLLT3* associated with an intermediate prognosis in ELN 2022 classification. For children also the t(9;11)(p21.3;q23.3) and t(11;19)(q23;p13) *KMT2A::ELL* or *KMT2A::ENL* are associated with an intermediate prognosis and t(1;11)(q21;q23)/*KMT2A::MLLT11* with a good prognostic

** poor prognosis in various studies but not retained in ELN 2022 classification

*** intermediate risk for ELN2022 but unfavorable in UK MRC

Complex Karyotype (CK) 3 or more unrelated abnormalities in the absence of recurring abnormalities such as : t(8;21), inv(16), t(16;16), t(v;11)(v;q23,3), t(6;9), inv(3), t(3;3) or t(9;22). Also exclude hyperdiploid with 3 or more trisomies or polysomies without structural abnormalities. Poor prognosis is still debated in peditric cases

Monsosomal Karyotype (MK) 2 or more autosomal monosomies or one autosomal monosomy with at least one structural abnormality excluding markers, rings and CBF abnormalities

[M] abnormalities classifying in the category AML myelodysplasia related (AML-MR) even without sign of myelodysplasia in cytology or previous history of myelodysplasia

recommended to identify these atypical cases. The use of molecular techniques should also include a search for rare or even unknown transcriptional isoforms. Even in the case of a classic t(15;17)(q24;q21), confirmation by reverse transcription–polymerase chain reaction is mandatory to identify the fusion transcript type and thus allow molecular follow-up [10].

Additional cytogenetic abnormalities (ACAs) are observed in approximately one-third of patients. The most frequent ACAs are +8, −7/7q, de(l9q), +11, and +21 [7,11], and their prognostic impact is still being debated [12].

Other *RAR* rearrangements (*RARr*) have been described in about 2% of patients with APL. These patients mainly present with an atypical M3 form. The *RARr* is mainly an *RARAr* with a non-*PML* partner recognised as APL, along with a variant RARA translocation (WHO-HAEM5) or APL with other *RARAr* [5,6]. The response to ATRA and ATO depends on the partner gene [10]. Very rare APLs present with rearrangement of *RARB* (3p24.2) or *RARG* (12q13.13) genes and are resistant to ATRA [13]. *PML::RARA*-negative APL requires an extensive genetic characterisation with careful chromosomal banding analysis (CBA); FISH with *RARA, RARB*, and *RARG* probes (if available); and, if possible, whole-transcriptomic or OGM analyses [2,9,10,14].

1.1.1.2. Core binding factor (CBF) abnormalities: t(8;21)(q22;q22.1)/RUNX1::RUNX1T1 and inv(16)(p13.1q22)/t(16;16)(p13.1;q22)/CBFB::MYH11. AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* and AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11* are referred to as CBF leukemias and are mostly observed, respectively, in the M2 and M4 with abnormal eosinophils (M4Eo) FAB subtypes. They represent 10% to 15% of adult AMLs, are more frequent in adolescents and young adults, and have a favourable prognosis [2,5,6,13].

RUNX1::RUNX1T1 and *CBFB::MYH11* fusions lead to alternative DNA binding and abnormal cellular localisation of CBF, respectively, resulting in transcription disruption that causes maturation arrest [15].

ACAs are detected in up to 60% of patients with CBF-AML [16]. Two or more ACAs are found in 20% of patients with CBF-AML [16]. Loss of a sex chromosome and del(9q) are the most frequent ACAs in patients with t(8;21)(q22;q22.1). By contrast, +22 is the most frequent ACA associated with inv(16)/t(16;16), followed by +8 and +21. Additionally, 3′*CBFB* (+/−5'*MYH11*) deletion can be found in 3–8% of patients and poses a challenge for FISH interpretation [17,18]. The association of a *CBFB::MYH11* fusion with a high-risk CA, as defined by the ELN, is rare (0.3%) [19]. Although the presence of ACAs does not alter the favourable prognosis of these entities according to the ELN-2022, several studies have seemed to show an impact for some of them. In patients with t(8;21), loss of Y appears to be associated with poorer OS [20]. Conversely, +22 seems to be associated with a better outcome for patients with *CBFB::MYH11* AML [20,21].

The number of mutations is higher in AML with t(8;21) than in AML with inv(16) and is also higher in adults than children. RTK/RAS signalling mutations are the most common variants observed, and such mutations include the *KIT, NRAS*, and *FLT3* genes. *FLT3* and *KIT* mutations have been associated with a slightly poorer prognosis than *WT1* and *NRAS* mutations [22–24]. Nevertheless, according to the ELN-2022, concomitant mutations do not change the risk categorisation [2].

1.1.1.3. 11q23/KMT2A rearrangements. *KMT2A* (formerly *MLL*) encodes a transcriptional coactivator of specific target genes, including many of the HOX family genes, and plays an essential role in early development and hematopoiesis. *KMT2A* rearrangements (*KMT2Ar*) occur in 2%–5%, 15–20%, and 47–55% of adult, pediatric, and infant AMLs, respectively. *KMT2Ar* is mainly associated with monoblastic/monocytic acute leukemias.

In the WHO-HAEM5 classification, *KMT2Ar* are now combined into a single entity. However, the ICC-2022 maintains a distinction between AML with t(9;11) rearrangement and AML with other *KMT2A* partners [5,6].

At least 94 partners have been identified to date. A genotype/phenotype correlation exists between the *KMT2A* translocation partner and the clinical subtypes of leukemia or the age of occurrence. *MLLT3* (*AF9*) is the most frequent partner in adult and pediatric AMLs, while *MLLT10* (*AF10*) is the main partner of *KMT2A* in infant AMLs. In more than 70% of patients with AML, the *KMT2Ar* involves *MLLT3* (*AF9*), *MLLT10* (*AF10*), *ELL, AFDN* (*AF6, MLLT4*), *ENL*, or *SEPT6* [25–29].

The ELN-2022 states that in adults, t(9;11)(p21.3;q23.3)/*KMT2A::MLLT3* is associated with an intermediate prognosis while other *KMT2Ar* are associated with a poor prognosis [2]. In children, in addition to t(9;11)(p21.3;q23.3)/*KMT2A::MLLT3*, t(11;19)(q23;p13) with either *ELL* (19p13.1) or *MLLT1(ENL)* (19p13.3) partners are associated with an intermediate prognosis [30].

ACAs are found in about half of *KMT2Ar*, with +8 being the most prevalent followed by +21q, +6, and +19 [29]; these ACAs do not impact OS. *KMT2Ar* AML presents with a low mutation burden, with *NRAS* and *KRAS* being the most commonly mutated genes [29].

Given the myriad of partners and the prognostic consequences of *KMT2Ar*, FISH with a separation probe and/or a molecular technique capable of detecting all partners of *KMT2A* is mandatory. Particular

attention must be paid to rearrangements involving *MLLT10* (10p12), which cannot be a simple reciprocal translocation due to the opposite centromeric/telomeric orientation of these genes. Complex rearrangements frequently produce an in-frame *KMT2A::MLLT10* fusion of these two genes with an opposite orientation. They can implicate a third breakpoint on the 11q region or a third chromosome [30]. The molecular insertion must be searched with a *KMT2A/MLLT10* double fusion probe and/or a suitable molecular analysis or RNA sequencing. Similarly, FISH fails to detect inv(11)(q23q23)/*KMT2A::USP2* in most patients, leading to an underestimation of its frequency [31]. Because this fusion gene derives from a short inversion within 11q23, the FISH profile may mimic a normal pattern. The alteration is only observed if the inversion is accompanied by a 3′ KMT2A deletion. Notably, 3′ *KMT2A* deletion at the chromosomal breakpoint occurs in approximately 10% of *KMT2r* AMLs.

1.1.1. 4. t(6;9)(p23;q34)/DEK::NUP214. The t(6;9)(p23;q34) translocation leading to *DEK::NUP214* fusion is a rare recurrent genetic abnormality detected in 0.9% to 1.8% of AMLs, mainly occurring in older children and young adults (median age of 12 and 35 years, respectively) [8,32,33]. These AMLs frequently show multilineage dysplasia and, in about half of cases, peripheral blood(PB)/bone marrow(BM) basophilia [5,6,34]. t(6;9) is most often the only clonal CA and is strongly associated with *FLT3*-ITD mutation and a poor prognosis [2,6,33–35].

1.1.1. 5. t(9;22)(q34;q11)/BCR::ABL1. AML with t(9;22)/*BCR::ABL1* fusion is now included as a permanent entity in the WHO-HAEMrevision [5]. Distinguishing between *de novo* AML with t(9;22) and chronic myeloid leukemia in a primary myeloid blast crisis can be difficult, requiring at least 20% blasts for diagnosis [5,6]. Neuendorff et al. proposed an algorithm for primary differential diagnosis. After excluding acute leukemia of ambiguous lineage by flow cytometry, a thorough history and physical examination is performed. In particular, unexplained leucocytosis, basophilia, and/or splenomegaly point toward the diagnosis of chronic myeloid leukemia blast crisis rather than AML. By contrast, prior signs of myelodysplastic syndrome (MDS) in PB or BM may support the diagnosis of (secondary) AML. Detection of p190-transcript and the presence of any *BCR::ABL1* fusion signal in < 100% of metaphases supports the diagnosis of AML rather than chronic myeloid leukemia [36]. In most cases, t(9;22)(q34.1;q11.2) is associated with ACAs such as −7 and +8, and a complex karyotype (CK). The reported incidence of AML with t(9;22) is < 1% [8,37]. These AMLs are associated with an adverse prognosis [2].

1.1.1.6. 3q26/MECOM rearrangements. The oncogene *MECOM (MDS1/EVI1* complex*)* is located at 3q26.2. In the WHO-HAEM5, AML with *MECOM* rearrangements (*MECOMr*) include not only the classical inv(3)(q21q26.2) and t(3;3)(q21;q26.2) but also AML with other 3q26.2/*MECOMr* [5].

In inv(3)(q21q26.2) and t(3;3)(q21;q26.2), the partner gene is *GATA2*, located at 3q21, and the *MECOMr* results in a juxtaposition of the distal *GATA2* enhancer (G2DHE) next to the *MECOM* oncogene, leading to *MECOM* overexpression and *GATA2* haploinsufficiency [38]. In other *MECOMr*, the most frequent partner genes are *RUNX1* (21q22) and *ETV6* (12p13). Other *MECOMr* leading to *MECOM* overexpression have been described: t(2;3) with several breakpoints on 2p, and t(3;3)/inv(3)/ins(3;3) not involving 3q21, t(3;5), t(3;6), t(3;7), t(3;8), or t(3;17) [39–41]. Gao *et al.* recently demonstrated *MECOM* overexpression in myeloid neoplasms with non-classic *MECOMr* [39].

The reported incidence of AML with inv(3)(q21q26.2)/t(3;3)(q21;q26.2) and *MECOMr* is 1 and 2% [8,42,43], and this percentage doubles when all *MECOMr* are included [8]. Monosomy 7, and del(7q) are the most common ACAs [44]. *MECOMr* AMLs are readily diagnosed by a *MECOM* break-apart FISH probe and are associated with a poor prognosis [2].

1.1.1. 7. t(8;16)(p11.2;p13.3)/KAT6A::CREBBP. AML with translocation t(8;16)(p11;p13) is a very rare abnormality (< 1% in adults and children, mainly neonates) resulting in *KATA6::CREBBP* gene fusion [45]. More than one-third of adult cases are post-cytotoxic therapy AML (pct-AML) [46]. Female predominance is observed, particularly in pct-AML. All patients present with acute monoblastic or myelomonocytic leukemia, frequently with erythrophagocytosis. Clinically, AML with t(8;16) is commonly associated with extramedullary disease and disseminated intravascular coagulation mimicking APL. Indeed, severe bleeding complications are the main cause of early death.

AML with t(8;16) in adults is associated with an adverse prognosis [2,46]. The prognosis is intermediate in children. Interestingly, one-third of neonates undergo spontaneous remission, and half of them remain in continuous remission [47].

1.1.1.8. 11p15/NUP98 rearrangements. Although rare (3%–5% of pediatric AMLs), 11p15 rearrangements involving the *NUP98* gene (*NUP98r*) are better known in children than in adults. Multiple partners have been described. The most frequent is *NSD1*; it is involved in the cytogenetically cryptic t(5;11)(q35;p15) [48], which may be associated with +8 [49]. The other most common translocation involves *KDM5A (JARID1A)* (12p13.3), which may be difficult to identify on CBA [50]. *NUP98::KDM5A* occurs in 2% of all pediatric AMLs (10% of pediatric cases of acute megakaryoblastic leukemia (AMKL)) [25,50,51]. Xie et al. recently reported *NUP98r* in 2.5% of adult patients with AMLs, of whom > 50% showed cryptic translocations detected only by FISH [52]. In this context, FISH using an *NUP98* break-apart probe is essential for the diagnosis of pediatric AML [49]. In adults, the morphologic, immunophenotypic, cytogenetic, and molecular features of AML with *NUP98r* are not well documented, and it would be important to include *NUP98* FISH testing in adult cohorts to clarify the incidence, partner genes, and molecular profiles of this entity. Notably, commercial *NUP98* probes are flanking distant dual-colour probes, and the interpretation of interphase FISH results alone can be difficult.

NUP98::NSD1 and *NUP98::KDM5A* are associated with a poor prognosis [53]. The prognosis of other rare *NUP98r* has not yet been established. In adults, only isolated case reports and series focusing on t(5;11)(*NUP98::NSD1*) [54] and t(7;11)/*NUP98::HOXA9* [55] have been reported. Although AMLs with *NUP98r* in adults were associated with a poor prognosis in all previous studies, these AMLs are assigned in the intermediate risk category in ELN-2022[2].

1.1.1.9. 12p abnormalities including the rare t(7;12)(q36;p13)/ETV6::MNX1. Abnormalities of the short arm of chromosome 12 (12p) have been associated with a poor prognosis in children [56,57]. Among 12p abnormalities, the rare, subtle, and often cryptic t(7;12)(q36;p13)/*ETV6::MNX1* has only been described in infants, with an incidence of 4.3% [58]. Because of the disparity of 7q molecular breakpoints, and the possibility of variant translocations, cryptic insertions, or deletion on the derivative 7q, FISH testing or RNASeq could be iof interest with respect to the transcript *ETV6::MNX1* [58,59].

The major ACA associated with this translocation is +19, which is found in 86% of cases. t(7;12)(q36;p13) is associated with an adverse prognosis [56,57] and a high relapse rate (77%) [58]. Therefore, FISH screening should be mandatory in infants under 2 years of age, especially those with +19 [59,60].

1.1.1. 10. inv(16)(p13.3q24.3)/CBFA2T3::GLIS2. Cryptic inversion of chromosome 16, inv(16)(p13.3q24.3)/*CBFA2T3::GLIS2*, was identified in 27% to 31% of non-Down Syndrome (DS) pediatric AMKL cases in previous studies [61,62]. Although half of reported cases were AMKL, this abnormality is not strictly limited to AMKL [63]. The median age is 1.5 years (range: 0.5–4 years), and patients show a female predominance and a poor prognosis [51,64,65]. Non-AMKL *CBFA2T3::GLIS2* AMLs are mostly observed in older children (median age, 12.4 years)

and also have a poor prognosis. Only half of patients with *CBFA2T3::GLIS2* AML achieve a complete response, and OS rates are very low (< 30%) [51,64,66].

ACAs such as chromosomal gains that lead to hyperdiploid karyotypes (mainly 47–49 chromosomes with +3 present in 20% of cases, followed by +21 and +Y) can be found in patients with *CBFA2T3::GLIS2* AML [51,66]. Interestingly, *CBFA2T3::GLIS2* AML has a specific immunophenotype characterised by high CD56 expression and low or no expression of HLA-DR, CD45, or CD38 antigens [66].

1.1.1. 11. t(16;21)(q24;q22)/RUNX1::CBFA2T3. The t(16;21)(q24;q22)*/RUNX1::CBFA2T3(RUNX1T3)* is a rare but recurrent CA [67]. One international collaborative study collected 23 cases, representing 0.2% of all pediatric AMLs [68]. The patients' median age was 6.8 years. ACAs were present in 85% of cases (+8, 42%;−Y, 43%). Overall, the outcomes were good, with a 0% cumulative incidence of relapse and a 4-year event-free survival rate of 77%.

AMLs with t(16;21)*/RUNX1::CBFA2T2* mimic AMLs with t(8;21)(q22;q22)*/RUNX1::RUNX1T1* in terms of morphology, immunophenotype, gene expression profile, and response to therapy [69].

1.1.1. 12. t(16;21)(p11;q22)/FUS::ERG. The t(16;21)(p11;q22) leading to *FUS*(16p11)::*ERG*(21q22) transcript is a very rare entity. This entity is mainly found in young adults (median age of 30 years) [70] and represents 0.4% of pediatric AMLs (median age of8.5 years) [68]. The prognosis is dismal (4-year event-free survival rate of 7%). In one study, ACAs were present in 71% of cases; they were mainly described as 'CK' and included +8 (19%) and +10 (13%) [68].

1.1.1. 13. t(1;22)(p13;q13)/RBM15::MLK1(MRTFA). The t(1;22)(p13;q13) translocation is a very rare abnormality (0.3% of pediatric AMLs) involving the *RBM15* (*OTT*) and *MKL1* (*MAL*) genes, which are located at 1p13.3 and 22q13.2, respectively. *RBM15::MLK1* AML only occurs in pediatric AMKLs (median age, 0.7 years; 5–10% of non-DS-AMKLs) [56,64,71,72]. This entity is associated with an intermediate outcome [51,65]. Reverse transcription–polymerase chain reaction or FISH analysis for *RBM15::MLK1* is essential for completion of CBA [64] because myelofibrosis can frequently lead to a karyotyping failure. Notably, a high proportion of normal metaphases can be seen in the CBA; these mainly present as a few ACAs with duplication of der(1)t(1;22) and gains of chromosomes 2, 6, 19, and 21, resulting in hyperdiploid karyotypes [64,71].

1.1.2. AML with cytogenetic abnormalities associated with MDS

The WHO-HAEM5 defines the entity 'AML, myelodysplasia-related/AML-MR', replacing the former 'AML with myelodysplasia-related changes (AML-MRC)'. In addition to the main changes to the definition (i.e. removal of morphological criteria and introduction of molecular abnormalities based on a set of eight genes), the definition also includes an update of the CA [5]: from the previous edition [32] only CK and unbalanced abnormalities remain. The ICC-2022 [6] also individualises a category according to cytogenetic abnormalities sufficient for the diagnosis of 'AML with MDS-related cytogenetic abnormalities' (Table 1). Both classifications contain a CK; chromosomes 5, 7, 12, and 17 unbalanced abnormalities; and isodicentric chromosome Xq (idic(Xq13)).

1.1.2.1. Chromosome 7 abnormalities. The most frequently reported autosomal monosomy in patients with AML is −7 (5% of AMLs in adults aged < 60 years) [8,73]. It is consistently associated with a poor prognosis [8,74]. In children, it should prompt a search for a genetic predisposition (see joint article).

Isolated del(7q) is less common in AML (approximately 2% of cases) [8]; it is more often part of a CK and associated with previous exposure to carcinogenic agents. Whereas the UK Medical Research Council guidelines [8] classify patients with del(7q) into the unfavourable risk group, the ELN-2022 [2] classifies them into the intermediate-risk group. Haploinsufficiency of tumour suppressor genes on chromosome 7 has been hypothesised as the mechanism underlying the pathogenesis of del(7q). Several studies have characterised commonly deleted regions and identified *EZH2, SAMD9L, CUX1, MLL3*, and *DOCK4* as possible candidates [75].

1.1.2.2. Chromosome 5 abnormalities. Approximately 5–10% of patients with AML harbour a 5q abnormality (monosomy 5, del(5q), or add(5q)) [8]. In contrast to MDSs, isolated del(5q) is a poor prognostic marker in AML, often denoting secondary AML arising from prior MDS. Two commonly deleted regions at 5q31 and 5q33 have been reported to be minimally necessary. These deletions cause loss of a large chromosomal region encompassing more than 30 genes, resulting in disease through haploinsufficiency of one or more genes including *RPS14*. Most del(5q) cases are often as part of a CK. Isolated del(5q) in AMLs appears to be a rare phenomenon and has not been well characterised.

1.1.2.3. Chromosome 17 abnormalities and AML with TP53 mutations. Chromosome 17 abnormalities (monosomy, deletion 17p, or i(17q)), which result in loss of *TP53,* are seen in approximately 5% of patients with AML, mainly adults [76]. *TP53*, located on 17p13, encodes the tumour suppressor protein p53, which is essential for cell cycle control and the DNA damage response. Although the WHO-HAEM5 and ICC-2022 state those chromosome 17 abnormalities are myelodysplasia-related, only the ICC-2022 identifies an entity with mutated *TP53. TP53* mutations occur in approximately 10% of patients with AML, and this frequency increases to about 30% in patients diagnosed with pct-AML [77]. Abnormalities of 17p and/or mutated *TP53* are strongly associated with CKs, with a frequency reaching 60% in patients with mutated *TP53* [78].

Loss-of-function mutations and deletions of *TP53* are associated with a very poor prognosis because of high refractoriness to conventional chemotherapy. Curiously, *TP53* is usually not mutated in patients with i(17q), but outcomes in these patients remain poor. This finding suggests that the adverse impact of 17p abnormalities may be attributable to either *TP53* loss or *TP53* mutation [79].

Consistent with this poor outcome, *TP53*-mutant AMLs are classified as poor risk in the ELN-2022. Notably, the outcome of patients with biallelic *TP53* alterations is generally worse [5].

In rare cases, *TP53* mutations can be germline (Li-Fraumeni syndrome), and AMLs with a germline *TP53* variant are classified as myeloid neoplasms with a genetic predisposition.

1.1.2.4. CKs. Currently, all the prognostic classifications (except the UK Medical Research Council) define a CK as 'three or more unrelated chromosomal abnormalities' [80]. The ELN-2022 [2] also specifies in the definition the absence of recurrent translocations or inversions (t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3), t(9;22)).

A CK was observed in approximately 8% of pediatric cases in the BFM98 trial [57] and in approximately 10%–12% of adult cases [8,42]. The incidence of a CK is also higher in patients older than 60 years (up to 23%) [81] with secondary AML (25%) or pct-AML (26.9%) [82]. Although CK has been associated with poor outcomes in adult AML, its prognostic value in pediatric AML remains controversial [56,57]. The vast majority of CKs are also *TP53*-mutated.

It should be noted that in the ELN-2022, CK clearly excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities [2].

1.1.2.5. Monosomal karyotype (MK). In 2008, Breems *et al.* defined an MK in AML for the first time [44]. An MK corresponds to two or more autosomal monosomies or a single autosomal monosomy combined with

at least one structural CA (excluding markers or rings and CBF abnormalities). Monosomy 7 is by far the most frequent chromosomal loss [83]. Most, but not all, MKs are CKs: 70% of CKs are MKs [44]. MKs account for 13% of all patients with AML and 22% of ≥ 60-year-old patients with AML [44,84]. An MK is independently associated with an unfavourable outcome and is included in the ELN-2022 [2]. MKs represent approximately 3% of cases of pediatric AML, but their prognostic value has not been established. In contrast to a UK research group [56], a German group found that MKs were associated with a poor prognosis, even after excluding monosomy 7 [57].

1.1.2. 6. idic(X). More frequent in patients with MDS, idic(X) has been reported in a few adult patients with AMLs, usually secondary to MDS. The idic(X)(q13) is often an isolated abnormality, although one or more copies of the idic may be present in the same cell. This suggests that idic (X)(q13) may be involved in early leukemogenesis. It is more often detected in women [85].

1.1.2.7. Other CAs. Deletion of the short arm of chromosome 12 (del (12p)) is a rare abnormality in adult AML but is not well defined. Conversely, 12p abnormalities in children have been associated with a poor outcome [56,57], as reviewed by Quessada *et al.* [30]. Some abnormalities are only described by one of the classifications: del(11q) and −13/del(13q) are mentioned in the WHO-HAEM5, while +8 and del (20q) appear only in the ICC-2022. Their frequency is low (often < 1%), and they are classified into the intermediate-risk group [2].

1.1.3. AML with normal karyotype and molecular abnormalities

A large subset of AML (approximately 40%–50% of adult AML and 25% of pediatric AML cases) is cytogenetically normal (CN-AML). Patients with CN-AML are considered to be at intermediate risk, but these AMLs actually constitute a heterogeneous group in which patient outcomes are highly variable because cryptic CAs associated with a poor prognosis can be found, mainly in children (see above). In recent years, next-generation sequencing (NGS) has made a considerable contribution to our understanding of this CN-AML group. In adults with CN-AML, the most prevalent mutations are identified in the NPM1, FLT3, CEBPA, NRAS, WT1, and *RUNX1* genes. In the pediatric TARGET-AML cohort, a specific mutational landscape of CN-AML was characterised by a higher prevalence of mutated *CEBPA, FLT3, GATA2, NPM1, PTPN11, TET2*, and *WT1* and a lower prevalence of mutated *KIT, KRAS*, and *NRAS* compared with abnormal karyotype-AML [86].

1.1.3.1. AML with NPM1 mutation. AML with *NPM1* mutation is a new WHO-HAEM5 subgroup that can be diagnosed regardless of the blast count (i.e. even if BM blasts are < 20%). *NPM1* mutation is the most frequent molecular abnormality in AML (approximately one-third of patients). This frequency increases to 45–65% in patients with CN-AML [87]. Isolated *NPM1* mutation is included in the ELN-2022 and is associated with a favorable prognosis. However, the detection of an adverse-prognosis CA [88] leads to reconsideration of the prognosis. Indeed, in the ELN-2022, patients with *NPM1* mutation and an adverse-prognosis CA may be stratified into the high-risk group.

1.1.3.2. AML with CEBPA mutation. AML with *CEBPA* mutation is the second subgroup of AML defined by a gene mutation in the WHO-HAEM5 and ICC-2022. Unlike AML with *NPM1* mutation, a blast count of > 20% is still required for the diagnosis of AML with *CEBPA* mutation in the WHO-HAEM5. The definition of AML with *CEBPA* mutation has changed in the WHO-HAEM5 to include biallelic (bi*CEBPA*) as well as single mutations located in the basic leucine zipper (bZIP) region. In contrast, in the ELN2022 only patients with in-frame mutations in the bZIP region are diagnosed as "AML with bZIP in frame mutated *CEBPA* mutation ", irrespective of the presence of a mono- or bi-allelic mutation, and associated with a good prognosis [5,6].

CEBPA mutations are evident in approximately 15% of patients with AML. The frequency of *CEBPA* mutations declines with age (1%–2% in patients aged > 60 years) [89]. *CEBPA* mutations are frequently associated with del(9q) [89]. CAs do not influence the good prognosis of *CEBPA* in the ELN-2022. In approximately 10% of cases, one of the *CEBPA* mutations can be a germline variant (see joint article).

1.1.3.3. AML with FLT3 mutation. FLT3 mutations are found in approximately 30% of patients with newly diagnosed AML [90] and are localised to two major regions of the protein: *FLT3* internal tandem duplication (*FLT3*-ITD) mutations in the juxta-membrane domain and *FLT3* tyrosine kinase domain (*FLT3*-TKD) mutations. *FLT3*-ITD mutations occur in approximately 25% of patients with AML, while *FLT3*-TKD mutations occur in only 7–10% of patients with AML. *FLT3*-ITD mutations are frequently associated with CAs such as t(15;17) or t(6;9). *FLT3*-TKD mutations are associated with inv(16)/t(16;16) or t(15;17) [89]. In the ELN-2022, only *FLT3*-ITD mutation occurring in the absence of a stratifying CA is an intermediate prognostic factor irrespective of the allelic ratio.

1.2. Blastic plasmacytoid dendritic cell (pDC) disorders

1.2.1. Blastic plasmacytoid dendritic cell (pDC) neoplasm (BPDCN)

BPDCN is a rare disease characterised by proliferation of tumour cells arising from precursors of pDCs. BPDCN can affect children and young adults, but it occurs more frequently in older men [5,91]. Myeloid neoplasms are diagnosed synchronously or prior to BPDCN in 20–30% of cases [92,93]. BPDCN is characterised by a very aggressive clinical course, with a median OS of 12–24 months after diagnosis [91].

The karyotype of BPDCN is abnormal in two thirds of cases. Among them, 90% exhibit a CK (≥3 CAs) showing predominantly recurrent deletions or monosomies over gains (mean of 6.5 CAs) [94,95]. Six major recurrent CAs, with frequent co-occurrence of three or more, have been described: del(5q) (72%), del(6q) (50%), −9 (28%), del(12p) (64%), del(13q)/−13 (64%), and del(15q)/−15. Such combinations are not described in AML harbouring a CK (or an MK), even in AML with cutaneous localisations [42].

Chromosomal microarray analyses (CMAs) have confirmed these complete or partial chromosomal losses. In a series of 21 patients, −9, −13, or −15 was detected in 67% of cases of BPDCN [96]. In addition, CMAs delineated the commonly deleted regions resulting in loss of transcription factors (12p13/*ETV6*, 7p12/*IKZF1*), glucocorticoid receptors (5q31/*NR3C1*), and genes involved in cell cycle regulation (9p21/*CDKN2A-B*, 13q14/*RB1*, and 12p13/*CDKN1B*) or immune responses (6q23/*IFNGR1* and *TNFAIP3*). CMA detects deletions of at least two of these loci in 90% of cases [97]. Large 17p deletions encompassing the *TP53* locus are observed in approximately 30% of cases, while focal losses of the 8q24 region are detected in 25–40% of cases [96–98].

Rearrangement of *MYC*/8q24 is the most frequent structural CA reported to date (8–38% of cases). In the largest series published, *MYC* rearrangement was detected in 38% of cases and was associated with older age, an immunoblastic morphology, and positivity for CD10 [99]. Remarkably, the 8q24 breakpoints are scattered over a large region of 3 Mb. *MYC* rearrangements mainly result from a t(6;8)(p21;q24) translocation that juxtaposes the enhancer of *RUNX2* (6p21) near the *MYC* locus, leading to MYC overexpression [100]. Despite its lack of specificity, t(6;8)(p21;q24) *RUNX2::MYC* is highly suggestive of the diagnosis of BPDCN. Other *MYC* partners distinct from *RUNX2* have been described in bands 3p25, 2p12, and Xq24 [101]. The prognostic impact of *MYC* rearrangement has not yet been clearly demonstrated.

The *MYB*/6q23 locus is also recurrently rearranged in up to 20% of cases of BPDCN [99]. It seems to occur with a high prevalence in children [102]. *MYB* rearrangements involve at least four partner genes (*ZFAT*/8q24, *PLEKHO1*/1q21, *DCPS*/11q24, and miR-3134/3p25), leading to *MYB* transcription deregulation [102]. The two most

Table 3
GFCH recommendations for cytogenetic management of acute myeloid leukemia and blastic plasmacytoid dendritic cell neoplasms at diagnosis: mandatory karyotype

Acute myeloid leukemia		
Karyotype result		**FISH**
Informative with recurrent abnormality	t(15;17)(q24;q21)/*PML::RARA*	[a] FISH **recommended** : ***KMT2A, NUP98, MECOM or ETV6*** - to check the involvement of genes - to help identify the partner
	t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*	
	inv(16)(p13.1q22)/t(16;16)(p13.1;q22)/*CBFB::MYH11*	
	t(6;9)(p23;q34)/*DEK::NUP214*	
	3q26 rearrangements *(MECOM)*[a]	
	11q23 rearrangements (*KMT2A*)[a]	
	11p15 rearrangements (*NUP98*) [a]	
	t(1;22)(p13;q13)/*RBM15::MKL1*	
	t(9;22)(q34;q11)/*BCR::ABL1*	
	t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP*	
	12p abnormalities *(ETV6)*[a]	
	Complex karyotype (CK)/ Monosomal Karyotype (MK)	
	-5/del(5q)/ -7/del(7q)/ i(17q)/t(17p)	
Normal or non-informative	- Normal karyotype ≥ 20 mitosis - Anomaly with intermediate prognosis not previously mentioned	**FISH mandatory** : - in all cases***: KMT2A*** - for children **: *NUP98*** - if <2 years old or +19 **: *ETV6*** **FISH recommended :** - in adults **: *NUP98***
	- Anomaly suggesting a variant translocation	**FISH mandatory** on the breakpoint involved in the suspected anomaly
	- Discordance with suggestive cytology	**FISH mandatory** on the anomaly suspected by cytology : Ex : *CBFB* or *CBFB::MYH11* if FAB M4 with eosinophils
	In case of **first failure** : -Retry bone marrow karyotype if possible - Blood karyotype if abnormal cells are circulating	**In case of second failure:** **FISH mandatory :** Cytology oriented -*PML::RARA* for APL - *RUNX1::RUNX1T1* (FAB AML M2) - *CBFB::MYH11* (FAB AML M4 with eosinophils) - *MECOM* (dysmegakaryopoiesis and/or thrombocytosis) Not Cytology oriented: See "Normal karyotype ≥ 20 mitosis or Anomaly with intermediate prognosis not previously mentioned" and: - *EGR1* (-5/del5q), -7q31 (-7/del7q) - for adults : *TP53* (del17p)

Blastic plasmacytoid dendritic cell neoplasm	
Karyotype result	**FISH**
	FISH **recommended** : large ***MYC*** and ***MYB*** (for children)

common *MYB* translocations are t(1;6)(q21;q23) *MYB::PLEK01* and t(6;8)(q23;q24) *MYB::ZFAT* [102,103].

In summary, the infrequent combinations of deletions and monosomies together with an *MYC* (or *MYB*) rearrangement constitute the peculiar cytogenetic signature of BPDCN.

A high number of somatic mutations mostly affecting epigenetic regulators (*TET2, ASXL1, IDH1, IDH2*, and *EZH2*), lymphoid differentiation (*IKZF1* and *ETV6*), and tumour suppressive function (*TP53* and *RB1*) and splicing (*ZRSR2* and *SRSF2*) have been described in BPDCN (for a review [98,104]).

The karyotype is of great interest in the diagnostic strategy of BPDCN and can discriminate BPDCN from standard AML or ALL. Complementary FISH analysis using a large *MYC* probe is recommended. An atypical *MYC* profile (3' deletion or 5' deletion) is common and highly suggestive of an *MYC* rearrangement. In children, we recommend performing FISH with an *MYB* probe.

1.2.2. Mature pDC proliferation (MPDCP) associated with myeloid neoplasms

MPDCP associated with myeloid neoplasms is a new WHO-HAEM5 entity that includes AML or chronic myelomonocytic leukemia associated with clonal proliferation of abnormal mature pDCs [5,98,105].

The incidence of AML associated with pDC expansion (pDC-AML) is estimated to be < 5% among all cases of AML [106]. In contrast to BPDCN, the CAs described in pDC-AML are similar to those described in classical AML. More specifically, the two most common CAs are del(7q) and +13, which are reported in 13% and 7% of cases, respectively [106]. Based on the ELN-2017 prognostic stratification, pDC-AML is classified into the high-risk group in 80% of cases, which is a higher percentage than that in classical AML [74]. Interestingly, a clonal relationship between leukemic blasts and pDCs was recently demonstrated [106,107].

A somatic mutation of the transcription factor *RUNX1* is detected in a large proportion (70%) of patients with pDC-AML. Other recurrently mutated genes are *SRSF2, ASXL1, TET2, DNMT3A, NRAS, PHF6, IDH1, SF3B1, TP53*, and *FLT3* [106].

2. Recommendations

CBA remains mandatory for the diagnosis of AML and PDC disorders [2,60] as well as for classification and risk stratification, and it is recommended when a new line of treatment is considered for patients who develop relapse. Results can and must be provided within 7 days.

The recommended culture time for karyotype analysis is at least overnight (up to 96 h) with the possibility of adding myeloid lineage stimulants such as granulocyte colony-stimulating factor.

BM or PB (the latter in patients with circulating blasts) must be used for CBA. In case of karyotype failure, a second sample collected before treatment initiation must be analyzed if possible.

FISH may be necessary in addition to the karyotype. The indications for FISH depend on the frequency of the abnormalities, the existence of cryptic or hidden stratifying abnormalities, the correlation with the morphological aspect, and the difficulty of detecting abnormalities in cases of poor mitosis quality or karyotype failure. Details are shown in Table 3.

3. Other cytogenomic techniques

Alternative testing strategies are now available, and advances in the development of high-throughput methods such as microarrays and NGS have improved our understanding of the AML pathogenesis.

3.1. NGS

In the routine clinical setting, NGS is commonly used with a targeted gene panel allowing the detection of not only gene mutations but also copy number abnormality. The results are relevant to classification, prognosis, and therapeutic decision-making. Targeted RNA sequencing is also performed in molecular laboratories to detect a large panel of fusion transcripts involving known AML driver genes.

NGS can also be used in a non-targeted manner to sequence the whole genome (detection of numerical and structural abnormalities), the whole exome, and the whole transcriptome. Whole-transcriptome sequencing allows the detection of all types of transcripts, products of gene fusions, and alternative splicing. For example, Wen *et al.* performed whole-transcriptome sequencing and discovered 134 fusion transcripts, 88 of which were novel, in AML samples, including 29 CN-AMLs [108]. The fusions were predominantly formed between adjacent genes on the same chromosome. In another study, targeted RNA sequencing resolved approximately 60% of rearrangements in cases where only one partner gene was known by cytogenetics, including rearrangements involving *RUNX1, ETV6, PDGFRB*, and *KMT2A* [109].

3.2. OGM

OGM is an emerging chip-based DNA technique with high resolution and no need for cell cultivation or DNA amplification. In theory, OGM has the ability to yield the information obtained from a combination of karyotyping, FISH, and CMA. There is currently little literature on this innovative technology specifically in AMLs.

Neveling *et al.* compared karyotyping/FISH and OGM in 52 hematological malignancies, 11 of which were AML [110]. They showed high concordance and identified some additional structural variants. In a study by Gerding et al. [111], OGM performed in 27 adults with AML and MDS was concordant with classical karyotyping in 93% of cases, and 61 additional variants could be detected. More recently, Levy *et al.* performed OGM on a larger cohort of 100 patients with AML. They showed that OGM provided new information in 13% of cases [112]. With respect to risk stratification of CAs, Creutzig et al. [26] compared CBA and FISH analysis with OGM in 24 cases of pediatric AML, and the results were concordant in 95% of cases.

Therefore, OGM is a powerful complementary tool in the cytogenetic diagnosis of AML, and it may replace FISH and CMA in the diagnostic approach.

4. Scores including cytogenetics

The ELN-2022 is one of the most widely used prognostic classifications. It is mainly based on the ICC-2022 and classifies adult patients (18–60 or ≥ 65 years of age) into three risk groups. The ELN-2022 combines cytogenetic and molecular abnormalities. In the updated ELN-2022, two new subtypes (*KAT6A::CREBBP* and other *MECOMr)* are included as adverse-risk cytogenetic events [2].

This prognostic classification is useful for survival stratification of patients with AML treated with intensive chemotherapy but is not suitable for use in conjunction with novel approaches such as targeted therapies (e.g. tyrosine kinase inhibitors) or venetoclax-based combination therapies, which will continue to improve outcomes in patients with AML. Future guidelines should take these developments into account. The most recent cytogenomic classification of childhood AML was established by the I-BFM group in 2012 [26].

5. Conclusion

The nosologic and prognostic classifications of AMLs place genetic abnormalities at the forefront. In 2023, CBA remains mandatory for AML diagnosis and pDC disorders [2,60] as well as for classification and risk stratification, and it is recommended when a new line of treatment is considered in patients with relapse. All the information given by the karyotype cannot be fully provided by any other technology at present. Molecular analysis, including searches for chimeric transcripts and mutations, is also mandatory to stratify patients, initiate tailored

therapy, and provide measurable disease monitoring [2].

CRediT authorship contribution statement

Audrey Bidet: Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Julie Quessada:** Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Wendy Cuccuini:** Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Matthieu Decamp:** Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Marina Lafage-Pochitaloff:** Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Isabelle Luquet:** Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Christine Lefebvre:** Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Giulia Tueur:** Writing – review & editing, Writing – original draft, Validation, Conceptualization.

Acknowledgments

We thank Nathalie Nadal, Nathalie Auger and Valentin Lestringeant for fruitful discussions and helpful comments

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