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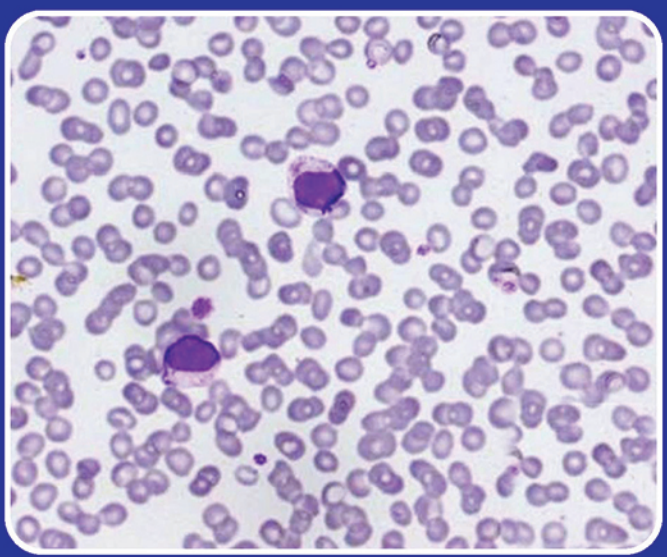
Recent Advances in HEMATOLOGY-4



Ishani Gupta
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CHAPTER 7

Pediatric Leukemias: Recent Updates

Sumayya Shah, Afshan Atta

INTRODUCTION

There have been numerous changes made to the classification of hematological cancers which have been collated in the latest 5th edition of the World Health Organization (WHO) Classification of Hematolymphoid Tumors. While a detailed discussion of all the updates would not be possible here, we will limit ourselves to those relevant to leukemias which affect the pediatric age group, that is, from birth to 17 years.

ACUTE LYMPHOBLASTIC LEUKEMIA

Pediatric acute lymphoblastic leukemia (ALL) is the success story of oncology and with innovations in diagnosis and therapeutic armamentarium, outlook is getting further refined and better with emphasis to minimize and mitigate the undesired long-term sequelae.

The last decade has witnessed great advances in our understanding of the genetic and biological basis of childhood ALL, the development of experimental models to probe mechanisms and evaluate new therapies, and the development of more efficacious treatment stratification. Genomic analysis has revolutionized our understanding of the molecular taxonomy of ALL, and these advances have led the push to implement genome and transcriptome characterization in the clinical management of ALL to facilitate more accurate risk stratification, and in some cases, targeted therapy.

Heritable Susceptibility to Acute Lymphoblastic Leukemia

Various studies denote that there is a genetic predisposition (Knudson hypothesis) to ALL, at least in a subgroup of cases. This evidence includes the presence of:

- Rare constitutional syndromes with greater risk for ALL such as Down syndrome (B-cell ALL) and ataxia-telangiectasia (T-cell ALL).

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- Familial cancer syndromes such as Li-Fraumeni syndrome.[1]
- Non-coding DNA polymorphisms that subtly influence the risk of ALL. Genome-wide association studies (GWAS) have identified at least 13 loci associated with ALL.[2-4]
- Genes harboring germline nonsilent variants presume to contribute toward the risk of sporadic ALL.

Prenatal Origin of Leukemia

Several lines of investigation indicate that a subset of childhood leukemia cases arise before birth. Chromosomal translocations, particularly *ETV6-RUNX1* may be detected at birth in blood spots and cord blood, years before the clinical onset of leukemia providing support for a multistep process of leukemogenesis. This is supported by genomic analysis of monozygotic, monochorionic twins concordant for leukemia showing genetic identity of initiating lesions and discordance for secondary genetic alterations indicating intertwin intrauterine transmission of leukemia. Evidence for in utero origin is strongest for *KMT2A*-rearranged and *ETV6-RUNX1* ALL.[5-7]

Genetics of B-cell Acute Lymphoblastic Leukemia

The most common form of ALL, B-cell ALL, comprises greater than 20 subtypes of variable prevalence according to age that are associated with distinct gene expression profiles and are driven by three main types of initiating genetic alteration:

1. Chromosomal aneuploidy
2. Rearrangements that deregulate oncogenes or encode chimeric transcription factors[8-10]
3. Point mutation

High hyperdiploidy (>50 chromosomes) is present in up to 30% childhood ALL and is associated with mutations in the RAS-pathway and has favorable outcome.[11] Low hypodiploidy (31–39 chromosomes) is present in approximately 1% of childhood ALL but in >10% of adult ALL. It is characterized by the deletion of *IKZF2* and by near-universal *TP53* which are inherited in approximately half the cases.[12,13] Near haploidy (24–30 chromosomes) is present in approximately 2% of pediatric ALL and is associated with RAS mutation (NF1) and deletion of *IKZF3*.[14] Both low hypodiploid and near-haploid ALL are associated with unfavorable outcomes. ALL with intra chromosomal amplification of chromosome 21 *(iAMP21)* is most common in older children and is associated with poor prognosis. t(12;21) (p13;q22) encoding *ETV 6-RUNX1* is the most common translocation in children and is associated with favorable prognosis.[15-17] Philadelphia chromosome formation due to t(9;22) (q34;q11.2) translocation encodes *BCR-ABL1* and is associated with unfavorable outcome, despite the fact that the prognosis has now been improved with help of combined chemotherapy and tyrosine kinase inhibition **(Table 1)**.

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TABLE 1: Genetic alterations, clinical features, age distribution, and genetic-based therapy among pediatric B- and T-acute lymphoblastic leukemia.

Category	Age	Description	Potential therapeutic implications
B-cell precursor acute lymphoblastic leukemia (ALL)			
Hyperdiploidy with more than 50 chromosomes	Children >> adults	Excellent prognosis; mutations in RAS signaling pathway and histone modifiers	Reduction of intensity
Near-haploid	Children-adults	24–31 chromosomes; poor prognosis; RAS-activating mutations; inactivation of *IKZF3*	BCL2 inhibitors
Low hypodiploid	Children < adults	32–39 chromosomes; poor prognosis; TP53 mutations (somatic and germline)	BCL2 inhibitors
iAMP21	Older children	Complex alterations of chromosome 21; requires high-risk therapy for good outcomes	Intensification of therapy
t(12;21) (p13;q22) encoding *ETV6-RUNX1*	Children >> adults	Excellent prognosis; cryptic rearrangement that is detectable by FISH	Reduction of intensity
ETV6-RUNX1–like	Children > adults	Absence of *ETV6-RUNX1* fusion; mutations in both *ETV6* and *IKZF1*	Reduction of intensity
t(1;19)(q23;p13) encoding *TCF3-PBX1*	Children-adults	Increased incidence in African Americans; favorable prognosis	
t(9;22)(q34;q11.2) encoding BCR-ABL1	Children << adults	Historically poor prognosis, improved with tyrosine kinase inhibitors; common deletions of *IKZF1*	ABL1 inhibitors, FAK inhibitors, rexinoids, BCL2 inhibitors
Ph-like	Children < adults	Kinase-activating lesions; poor outcome; potentially amenable to kinase inhibition	ABL1 inhibitors, JAK inhibitors, PI3K inhibitors, BCL2 inhibitors
CRLF2 rearranged *(IGH-CRLF2; P2RY8-CRLF2)*	Children < adults	Common in Down syndrome and Ph-like ALL; associated with *IKZF1* deletion and *JAK1/2* mutation	JAK inhibitors, BCL2 inhibitors
KMT2A (MLL) rearranged	Infants >> children-adults	Common in infant ALL; dismal prognosis; few co-operating mutations, commonly in RAS signaling pathway	DOT1L inhibitors, menin inhibitors, proteasome inhibitors, HDAC inhibitors, BCL2 inhibitors

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Category	Age	Description	Potential therapeutic implications
DUX4 rearranged and *ERG* deregulated	Children-adults	Distinct gene expression profile; most have focal ERG deletions and favorable outcome despite *IKZF1* alterations	Reduction of intensity
MEF2D rearranged	Children-adults	Distinct gene expression profile; potential sensitivity to HDAC inhibition	HDAC inhibitors
ZNF384 rearranged	Children	Pro-B-ALL phenotype; expression of myeloid markers; *FLT3* increased expression	FLT3 inhibitors
PAX5alt	Children > adults	PAX5 fusions, mutation, or amplifications; prognosis intermediate	
PAX5 P80R	Children < adults	Frequent signaling pathway alterations	Kinase inhibitors
IKZF1 N159Y	Children-adults	Rare; unknown prognosis	FAK inhibitors, rexinoids
NUTM1 rearranged	Children	Exclusively in children; rare; prognosis excellent	HDAC inhibitors, bromodomain inhibitors
t(17;19)(q22;p13) encoding TCF3-HLF	Children-adults	Rare; dismal prognosis	BCL2 inhibitors
Rearranged *BCL2/MYC*	Children << adults	Poor prognosis	
T-lineage acute lymphoblastic leukemia			
TAL1 deregulation	Children-adults	Enrichment of mutation in PI3K signaling pathway	PI3K inhibitors, nelarabine, BCL2 inhibitors nelarabine, BCL2 inhibitors
TLX3 deregulation	Children-adults	Poor prognosis; frequent co-operating mutation in ubiquitination and ribosomal genes	
HOXA deregulation	Children-adults	Frequent mutations in JAK-STAT pathway, *KMT2A* rearrangements	JAK inhibitors, nelarabine, BCL2 inhibitors
TLX1 deregulation	Children-adults	Favorable prognosis	Nelarabine, BCL2 inhibitors
LMO2/LYL1 deregulation	Children-adults	Poor prognosis; enriched for ETP-ALL, frequent co-operating mutation in JAK-/STAT	JAK inhibitors, nelarabine, BCL2 inhibitors

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Category	Age	Description	Potential therapeutic implications
NKX2-1 deregulation	Children-adults	Frequent co-operating mutation in ribosomal genes	Nelarabine, BCL2 inhibitors
NUP214-ABL1 with 9q34 amplification	Children-adults	Neutral prognosis, in contrast to kinase-driven B-ALL; potentially amenable to tyrosine kinase inhibition	ABL1 inhibitors, nelarabine, BCL2 inhibitors
Early T-cell precursor ALL	Children-adults	Poor prognosis; genetically heterogeneous with mutations in hematopoietic regulators, cytokine and RAS signaling, and epigenetic modifiers	JAK inhibitors, BCL2 inhibitors

(FISH: fluorescence in situ hybridization; ALL: acute lymphoblastic leukemia; HDAC: histone deacetylase)
Source: Inaba H, Mullighan CG. Pediatric acute lymphoblastic leukemia. Haematologica 2020; 105(11):2524-39.

Kinase-driven Subtypes

Of therapeutic relevance are the two-kinase-driven subtypes; Philadelphia chromosome-positive and Philadelphia chromosome like ALL. Their frequency increases with age and they account for 25% and 20% respectively of adult ALL.[18]

Genetic Basis of T-cell Acute Lymphoblastic Leukemia

Childhood T-cell ALL is characterized by recurrent alterations in 10 pathways, but in most cases, three pathways are abnormally regulated.

1. Expression of transcription factors of T-cell lineage.
2. Signaling of NOTCH/MYC.
3. Cell cycle control.[19-21]

MIXED-PHENOTYPE ACUTE LEUKEMIA

It is uncommon, representing only 2–5% of pediatric leukemias. Mixed-phenotype acute leukemia (MPAL) is defined as acute leukemia expressing a combination of antigens not restricted to a single lineage with the following categories; B/myeloid NOS and T/myeloid NOS in addition to two genetic subgroups of MPAL; that with t(9;22) (q34.1;q11.2), *BCR–ABL 1* and that with t(v;11q23.3), *KMT2A* rearranged. Genetic characterization of pediatric MPAL revealed that rearrangement of ZNF 384 is common in B/myeloid MPAL and biallelic WT1 alterations are common in T/myeloid MPAL. Such genetic alterations are consistent with the results of a retrospective multinational study showing that ALL type therapy is more effective than acute myeloid leukemia (AML) or combined type treatment in patients with MPAL.

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Risk Assignment for Treatment (Table 2)

Adverse Prognostic Factors

- Age (infant or ≥ 10 years)
- WBC count (≥50 × 10^5/L)
- Involvement of the CNS
- T-cell immunophenotype
- Race (Black or Hispanic)
- Male sex

TABLE 2: Risk factors in pediatric acute lymphoblastic leukemia.

Factor	Better	Worse
Patient and clinical characteristics		
Age at diagnosis	1 to <10 years	<1 year or ≥10 years
Sex	Female	Male
Race	Caucasian Asian	African American, Hispanic
Down syndrome	No	Yes
WBC counts at diagnosis	<50 × 10^9/L	≥50 × 10^9/L
CNS involvement at diagnosis	CNS 1	CNS 2 and CNS 3, traumatic tap with blasts
Testicular involvement	No	Yes
Immunophenotype	B-ALL	T-ALL
Cytogenetic and genetics		
	High hyperdiploidy (51–65 chromosomes)	Hypodiploidy (<44 chromosomes)
	ETV6-RUNX1: t(12;21) (p13.2;q22.1)	*KMT2A* rearrangement: t(v;11q23.3)
	NUMT1 rearrangement	*BCR-ABL1*: t(9;22)(q34.1;q11.2) (Ph+)
		BCR-ABL1-like (Ph-like)
		TCF3-HLF: t(17;19)(q22;p13)
		MEF2D rearrangement
		Intrachromosomal amplification of chromosome 21 (iAMP21)
		BCL2 or *MYC* rearrangements
Minimal residual disease		
	Negative	Positive
	Continuously decreasing and becoming negative	Increasing and/or persistently positive while monitored

(WBC: white blood cell; CNS: central nervous system; ALL: acute lymphoblastic leukemia; Ph: philadelphia chromosome)

Source: Inaba H, Mullighan CG. Pediatric acute lymphoblastic leukemia. Haematologica 2020; 105(11):2524-39.

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Better Prognosis Factors

- Hyperdiploidy (>50 chromosomes)
- *ETV6-RUNX1*
- Low WBC counts

Worst Prognostic Factors

- Hypodiploidy (< 44 chromosomes)
- Ph-positive or Ph-like ALL/*KMT2A/MEF2D or BCL2/MYC* rearrangements

Treatment

In the last decade, molecularly targeted agents and immunotherapy have emerged as novel therapeutic strategies. Immunotherapy can be provided as antibody-based therapy, e.g., blinatumomab or inotuzumab ozogamicin or T-cell-based therapy, i.e., chimeric antigen receptor T (CAR-T) cells that have enhanced the response rate and the results in patients with relapsed/refractory B-ALL. Antibodies and CAR-T cells against T-ALL are also under investigation **(Fig. 1)**.

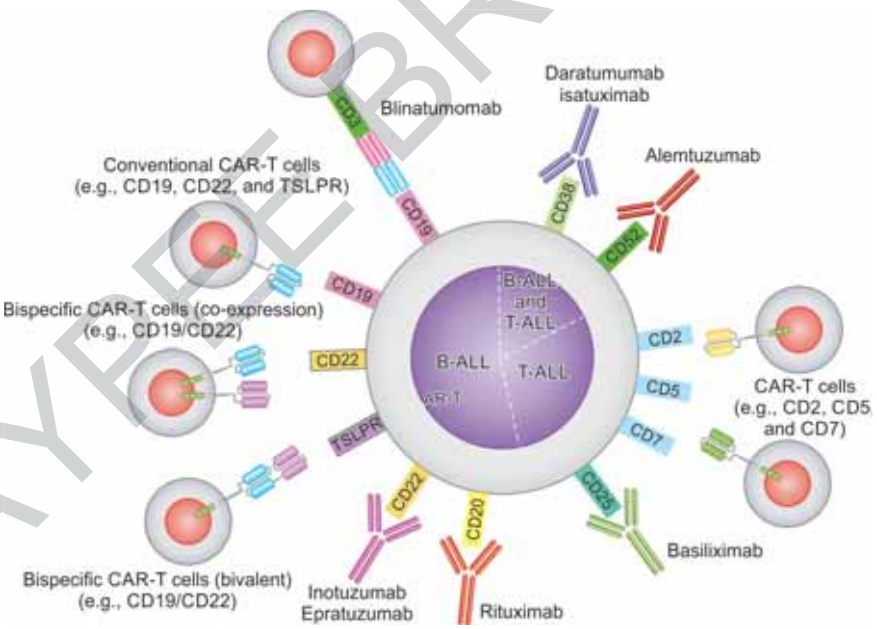

FIG. 1: Immunotherapy in acute lymphoblastic leukemia.

(CAR-T cells: chimeric antigen receptor T cells; ALL: acute lymphoblastic leukemia; TSLPR: thymic stromal lymphopoietin receptor.

Source: Inaba H, Mullighan CG. Pediatric acute lymphoblastic leukemia. Haematologica 2020;105(11): 2524-39.

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ACUTE MYELOID LEUKEMIA

The risk of developing AML in most cases is biological rather than environmental with the only established pediatric AML cause being in utero exposure to ionizing radiation.[22-24] Other exposures for example, maternal chemical exposure and parental age have only limited evidence supporting their association with AML.[25] Down syndrome is the most common genetic risk factor followed by diseases associated with DNA repair deficiencies, such as Fanconi anemia and ataxia telangiectasia. The AML to ALL ratio is 1:4 except in neonatal period.

Biology of Pediatric Acute Myeloid Leukemia

The latest WHO classification allows for a much finer differentiation, with more accurate prognostic correlations. The major categories are AML with defining genetic abnormalities and AML, defined by differentiation **(Box 1)**.

BOX 1 Acute myeloid leukemia.

Acute myeloid leukemia with defining genetic abnormalities

- Acute promyelocytic leukemia with *PML::RARA* fusion
- Acute myeloid leukemia with *RUNX1::RUNX1T1* fusion
- Acute myeloid leukemia with *CBFB::MYH11* fusion
- Acute myeloid leukemia with *DEK::NUP214* fusion
- Acute myeloid leukemia with *RBM15::MRTFA* fusion
- Acute myeloid leukemia with *BCR::ABL1* fusion
- Acute myeloid leukemia with *KMT2A* rearrangement
- Acute myeloid leukemia with *MECOM* rearrangement
- Acute myeloid leukemia with *NUP98* rearrangement
- Acute myeloid leukemia with *NPM1* mutation
- Acute myeloid leukemia with *CEBPA* mutation
- Acute myeloid leukemia, myelodysplasia-related
- Acute myeloid leukemia with other defined genetic alterations

Acute myeloid leukemia, defined by differentiation

- Acute myeloid leukemia with minimal differentiation
- Acute myeloid leukemia without maturation
- Acute myeloid leukemia with maturation
- Acute basophilic leukemia
- Acute myelomonocytic leukemia
- Acute monocytic leukemia
- Acute erythroid leukemia
- Acute megakaryoblastic leukemia

Source: Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022;36:1703-19.

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Transient Abnormal Myelopoiesis

It is seen in neonatal period, more commonly in cases of Down syndrome. About 10% of children with Down syndrome develop transient abnormal myelopoiesis (TAM).[26-28] Majority remit by 3 months. Dysplastic features are common. Mutations in *GATA-1* gene is incriminated.

Core-binding Factor Leukemia

Two common cytogenetic abnormalities make up the largest group of core-binding factor (CBF) leukemias; t(8;21) (q22;q22) and inv(16) (p13.1q 22) representing approximately 15% and 6% of pediatric AML cases, respectively.

Acute Promyelocytic Leukemia with PML::RARA Fusion Gene

Almost every case (95%) of acute promyelocytic leukemia (APL) has a characteristic t(15;17) (q22;q21) translocation which results in the fusion of promyelocytic leukemia (PML) (role in transcriptional regulation and tumor suppression) and *RARA* genes (role in differentiation process). When these two genes fuse, the resultant protein prevents both physiological functions and conversely the fusion protein binds to DNA and acts in a dominant negative fashion to repress gene expression as well as nuclear body formation. Though APL is considered to be universally fatal, this unique biology allows the use of targeted therapies that makes APL have a more favorable prognosis.

Therapy-related Myeloid Neoplasms

It is less common in children as by the time therapy-related myeloid neoplasms (t-AML) develops, the patient has reached adulthood. Though t-AML is not defined by any specific set of genetic abnormalities, there are trends that are arising. The use of certain chemotherapy drugs, especially anthracyclines and etoposide are highly correlated with the development of t-AML with chromosomal abnormalities involving 11q23.

Acute Myeloid Leukemia with CEPBA Mutation

The CCAAT enhancer-binding protein family (C/EBP) is made up of several related transcription factors, the α isoform of which is commonly mutated in pediatric AML.

Treatment and Prognostic Considerations for Pediatric AML

When treating AML, there are many factors that need to be considered:

- Urgency
- Efficacy

Though advances have been made in the treatment of pediatric AML, the most effective therapies are profoundly toxic even when administered properly. Therefore, it is imperative that measures be taken to maximize efficacy and minimize toxicity.

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Favorable Prognostic Indicators

Core binding factor AML represents one of the largest AML subgroups associated with favorable prognosis. Similarly, APL with the standard cytogenetics is also associated with good outcome.

Adverse Prognostic Indicators

Certain translocations including t(10;11) (p12;q23), t(6;9) (p23;q34), inv(3) (q21126.2) are poor prognostic markers. t-AML is always considered to have adverse prognosis.

MYELOPROLIFERATIVE NEOPLASMS

These include all the diseases mentioned in previous editions with the addition of juvenile myelomonocytic leukemia (JMML) **(Box 2)**. They have a chronic phase (CP) which transforms into an accelerated phase (AP) and then a blast phase (BP) with acquisition of more and more cytogenetic and/or molecular mutations.

Chronic Myeloid Leukemia

This is the most common of the myeloproliferative neoplasms (MPNs), the hallmark of which is the *BCR::ABL1* fusion gene resulting from t(9;22) (q34;q11). Majority of the cases present in CP which then progresses to BP, with or without passing through AP. With the advent of tyrosine kinase inhibitors (TKIs) and disease monitoring, longer progression-free intervals have become the norm with an overall 10-year survival rate of 80–90%. With resistance due to *ABL1* kinase mutations and/or additional cytogenetic mutations and development of BP recognized as important disease characteristics,[29,30] AP has become superfluous and has been removed in this classification with more stress placed on high-risk features associated with CP progression and TKI resistance. BP criteria include (1) ≥20% myeloblasts in peripheral blood or bone marrow; or (2) extramedullary proliferation of blasts; or (3) increased lymphoblasts in peripheral blood or bone marrow.

BOX 2 Myeloproliferative neoplasms.

- Chronic myeloid leukemia
- Polycythemia vera
- Primary myelofibrosis
- Essential thrombocythemia
- Chronic neutrophilic leukemia
- Chronic eosinophilic leukemia
- Juvenile myelomonocytic leukemia
- Myeloproliferative neoplasm, not otherwise specified

Source: Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022;36:1703-19.

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The exact cutoff percentage of lymphoblasts and significance of increased lymphoblasts is not yet known.

BCR::ABL1-negative Myeloproliferative Neoplasms

There have been some small changes in the diagnostic criteria of polycythemia vera (PV), primary myelofibrosis (PMF) and essential thrombocythemia (ET).

Measurement of increased red cell mass using ^{51}Cr-labeled red cells has been omitted as a diagnostic criterion since this test is rarely done in routine practice. Increased hemoglobin/hematocrit with panmyelosis and pleomorphic mature megakaryocytes in the marrow along with *JAK2 V617F* or *JAK2 exon 12* mutations are still major diagnostic criteria. The criteria for diagnosing ET, PMF, and chronic neutrophilic leukemia (CNL) remain the same.

Major changes have been made in the diagnosis of chronic eosinophilic leukemia (CEL): (1) persistent hypereosinophilia for 4 weeks instead of 6 months. (2) Both clonality and atypical bone marrow morphology (e.g., erythroid or megakaryocytic dysplasia) required. (3) Increased blasts as a substitute for clonality have been abolished. These updates further clarify the difference between CEL and conditions such as idiopathic hypereosinophilic syndrome and hypereosinophilia of unknown significance.[31] With refinement of diagnostic criteria and greater understanding of CEL in relation to other diseases with eosinophilia, the adjunct "not otherwise specified" has been eliminated.

Myeloproliferative neoplasm, not otherwise specified (MPN-NOS) is used for cases with morphological, laboratory, and molecular features of MPN which do not fit into a particular subtype or fit into more than one subtype.

Juvenile Myelomonocytic Leukemia

Juvenile myelomonocytic leukemia has now been classified as a myeloproliferative neoplasm of childhood with some revisions to its diagnostic criteria which include (1) *KMT2A* rearrangements excluded, (2) monosomy 7 removed as a cytogenetic criterion, and (3) greater weightage given to diagnostic molecular tests especially those that indicate RAS-pathway activation. Risk stratification and therapeutic approach depend on the genetics of each case with those showing germline CBL mutations occasionally undergoing spontaneous remission while those having somatic mutations involving *PTPN11* and germline pathogenic variants involving neurofibromatosis type 1 behaving aggressively. The classification of JMML as an MPN signifies the lack of true dysplasia in this condition.

MYELODYSPLASTIC NEOPLASMS

Myelodysplastic syndromes have been renamed as myelodysplastic neoplasms, although still abbreviated as MDS, emphasizing their malignant disposition, and bringing them in line with MPN. They are now

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divided into those having defining genetic abnormalities and those that are morphologically defined **(Table 3)**. This rearrangement bases risk stratification on schemes like the Revised International Prognostic Scoring System for MDS (IPSS-R) by focusing on genetic basis of disease.[32] Also, clearer terms are used to better differentiate MDS with low blasts (MDS-LB) and MDS with increased blasts (MDS-IB) with the maintenance of previous cutoff values.

TABLE 3: Classification and defining features of myelodysplastic neoplasms (MDS).

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<2% PB and <5% BM	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and SF3B1 mutation[a] (MDS-SF3B1)		Absence of 5q deletion, monosomy 7, or complex karyotype	SF3B1
MDS with biallelic TP53 inactivation (MDS-biTP53)	<20% PB and BM	Usually complex	Two or more TP53 mutations, or 1 mutation with evidence of TP53 copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<2% PB and <5% BM		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	2–4% PB or 5–9% BM		
MDS-IB2	5–19% PB or 10–19% BM or Auer rods		
MDS with fibrosis (MDS-f)	2–19% PB; 5–19% BM		

[a]Detection of ≥15% ring sideroblasts may substitute for SF3B1 mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.

[b]By definition, ≤25% bone marrow cellularity, age adjusted.

(PB: peripheral blood; BM: bone marrow; cnLOH: copy neutral loss of heterozygosity)

Source: Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022;36:1703-19.

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Myelodysplastic Syndrome with Defining Genetic Abnormalities

This comprises MDS with low blasts and isolated 5q deletion (MDS-5q), MDS with low blasts and *SF3B1* mutation (MDS-SF3B1), and MDS with biallelic *TP53* inactivation (MDS-biTP53).

MDS-5q diagnostic criteria remain the same. An additional *SF3B1* or *TP53* mutation (not multi-hit) does not alter a diagnosis of MDS-5q, although their presence is considered to change the behavior and/or prognosis of disease.

MDS-SF3B1 is now considered a separate entity which includes nearly all cases of MDS with ≥5% ring sideroblasts.[33] For cases with wild-type SF3B1 and ≥15% ring sideroblasts, the term MDS with low blasts and ring sideroblasts can still be used, allowing uncommon MDS cases with driver mutations in other *RNA* splicing genes to be covered as well.

Myelodysplastic Syndrome, Morphologically Defined

Hypoplastic MDS (MDS-h) has now been identified as a distinct disease subtype in the latest WHO classification. It involves a T-cell-mediated immune attack on hematopoietic stem cells with oligoclonal proliferation of $CD8^+$ cytotoxic T-cells producing TNF-α and/or IFN-γ. There are many similarities seen among MDS-h, paroxysmal nocturnal hemoglobinuria (PNH) and aplastic anemia (AA), including an association with clonal hematopoiesis (CH).[34-36] MDS-h also needs to be differentiated from patients having germline pathogenic mutations in *GATA2, DDX41*, Fanconi anemia (FA) or telomerase complex genes as these also have hypoplastic marrows and progress to MDS and/or AML but do not respond to immunosuppressive agents unlike MDS-h which shows a good response to anti-thymocyte globulin (ATG), a drug typically used in AA.

Specifying single lineage or multiple lineage dysplasia has become redundant as the number of cell lines involved keeps changing and reflects clonal evolution rather than different MDS subtypes. The category of MDS, unclassifiable has also been eliminated due to upgradation of the MDS classification scheme and inclusion of clonal cytopenia of undetermined significance (CCUS).

Myelodysplastic Syndrome and Acute Myeloid Leukemia

There have been several calls to redefine the blast percentage in bone marrow which differentiates MDS-IB2 from AML for various reasons and due to new therapies that are effective in patients currently diagnosed as MDS or AML with 10–30% blasts.[37-39] Some of the practical problems justifying this review include (1) myeloid neoplasms exist on a biological spectrum, making any blast cutoff discretionary; (2) blast counts differ due to sampling variations/error and subjective assessments; and (3) there is no gold standard for blast enumeration and orthogonal tests often give mismatched results. Combining MDS-IB2 and AML and lowering the blast percentage to 10% (forming a new

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TABLE 4: Childhood myelodysplastic neoplasms (MDS).

	Blasts
Childhood MDS with low blasts	<2% PB; <5% BM
Hypocellular	
Not otherwise specified	
Childhood MDS with increased blasts	2–19% PB; 5–19% BM

(PB: peripheral blood; BM: bone marrow)

Source: Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022;36:1703-19.

group of MDS/AML) had the same objections as above as well as danger of overtreatment. Therefore, a 20% blast cutoff was maintained to distinguish MDS from AML except for cases of AML with defining genetic mutations, which can have any blast percentage. However, from a treatment and clinical trial design viewpoint, MDS-IB2 is considered equivalent to AML.

Childhood Myelodysplastic Neoplasms

These are clonal hematopoietic stem cell cancers found in children and adolescents resulting in ineffective hematopoiesis, cytopenia(s) and risk of evolution into AML. This group does not include JMML, myeloid proliferations of Down syndrome and post-cytotoxic therapy MDS. The qualifier, childhood, signifies that this type of MDS is biologically separate from adult MDS,[40,41] the exact pathogenesis still incompletely understood.

"Refractory cytopenia of childhood (RCC)" is now known as childhood MDS with low blasts (cMDS-LB) and has two subtypes: childhood MDS with low blasts, hypocellular; and childhood MDS with low blasts, not otherwise specified (NOS) **(Table 4)**. Cases need to be carefully assessed for dysplasia in hematopoietic cell lines as majority (80%) show bone marrow hypocellularity and features resembling severe AA and other bone marrow failure syndromes (BMFS).[42] Patients with monosomy 7, 7q deletion or complex karyotype are treated with hematopoietic stem cell transplant due to high risk of evolution to AML while patients with normal karyotype or trisomy 8 have an indolent course.

Childhood MDS with increased blasts (cMDS-IB) shows ≥5% blasts in bone marrow or ≥2% blasts in peripheral blood. Acquired cytogenetic aberrations andthway mutations are more common in it compared with cMDS-LB.[43,44]

MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS

The latest edition of the WHO classification has significant modifications in the chronic myelomonocytic leukemia (CMML) diagnostic criteria as well as terminology changes for other MDS/MPN types **(Box 3)**.

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BOX 3 Myelodysplastic/myeloproliferative neoplasms.

- Chronic myelomonocytic leukemia
- Myelodysplastic/myeloproliferative neoplasm with neutrophilia
- Myelodysplastic/myeloproliferative neoplasm with SF3B1 mutation and thrombocytosis
- Myelodysplastic/myeloproliferative neoplasm, not otherwise specified

Source: Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022;36:1703-19.

Chronic Myelomonocytic Leukemia

The absolute monocyte count for sustained peripheral blood monocytosis is reduced from 1.0×10^9/L to 0.5×10^9/L, helping encompass cases previously named as oligomonocytic CMML.[45-47] Dysplasia in at least one lineage plus clonal cytogenetic or molecular abnormality is required for diagnosis when absolute monocyte count is between 0.5×10^9/L – 1.0×10^9/L. Abnormal separation of peripheral blood monocyte subsets has been introduced as a new supporting criterion **(Box 4)**.[48,49] Further research is required to classify those with unexplained clonal monocytosis[50] who do not fulfil the new CMML diagnostic criteria.

Chronic myelomonocytic leukemia has two subtypes, divided based on white cell count: (1) myelodysplastic CMML (MD-CMML) with WBC count $<13 \times 10^9$/L; and (2) myeloproliferative CMML (MP-CMML) with WBC count $\geq 13 \times 10^9$/L. The latter usually shows activating RAS-pathway mutations and adverse prognosis.[51] The subgroup of CMML-0 has been removed due to no/limited prognostic significance.[52,53]

Terminology Updates

Diagnostic criteria of other MDS/MPNs remain mostly the same. Atypical chronic myeloid leukemia (CML) has been renamed as MDS/MPN with neutrophilia, thus emphasizing the MDS/MPN nature of the disease and avoiding confusion with CML. MDS/MPN with ring sideroblasts and thrombocytosis has been replaced by the term MDS/MPN with SF3B1 mutation and thrombocytosis but can still be used for cases with wild-type *SF3B1* mutation and ≥15% ring sideroblasts. MDS/MPN, unclassifiable is now known as MDS/MPN, not otherwise specified, being part of an attempt to omit the paradoxical qualifying term of "unclassifiable" from the whole classification.

MASTOCYTOSIS

It has three types: (1) systemic mastocytosis (SM), (2) cutaneous mastocytosis (CM), and (3) mast cell sarcoma (MCS) **(Box 5)**.[54]

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BOX 4 Diagnostic criteria of chronic myelomonocytic leukemia (CMML).

Prerequisite criteria:

- Persistent absolute (≥0.5 × 10^9/L) and relative (≥10%) peripheral blood monocytosis
- Blasts constitute <20% of the cells in the peripheral blood and bone marrow[a]
- Not meeting diagnostic criteria of chronic myeloid leukemia or other myeloproliferative neoplasms[b]
- Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with tyrosine kinase fusions[c]

Supporting criteria:

- Dysplasia involving ≥1 myeloid lineages[d]
- Acquired clonal cytogenetic or molecular abnormality
- Abnormal partitioning of peripheral blood monocyte subsets[e]

Requirements for diagnosis:

- Prerequisite criteria must be present in all cases
- If monocytosis is ≥1 × 10^9/L: One or more supporting criteria must be met
- If monocytosis is ≥0.5 and <1 × 10^9/L: Supporting criteria 1 and 2 must be met

Subtyping criteria:

- Myelodysplastic CMML (MD-CMML): WBC <13 × 10^9/L
- Myeloproliferative CMML (MP-CMML): WBC ≥13 × 10^9/L

Subgrouping criteria (based on percentage of blasts and promonocytes):

- CMML-1: <5% in peripheral blood and <10% in bone marrow.
- CMML-2: 5–19% in peripheral blood and 10–19% in bone marrow.

[a]Blasts and blast equivalents include myeloblasts, monoblasts, and promonocytes.

[b]Myeloproliferative neoplasms (MPN) can be associated with monocytosis at presentation or during the course of the disease; such cases can mimic CMML. In these instances, a documented history of MPN excludes CMML. The presence of MPN features in the bone marrow and/or high burden of MPN-associated mutations (JAK2, CALR or MPL) tends to support MPN with monocytosis rather than CMML.

[c]Criteria for myeloid/lymphoid neoplasms with tyrosine kinase fusions should be specifically excluded in cases with eosinophilia.

[d]Morphologic dysplasia should be present in ≥10% of cells of a hematopoietic lineage in the bone marrow.

[e]Based on detection of increased classical monocytes (>94%) in the absence of known active autoimmune diseases and/or systemic inflammatory syndromes.

Source: Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022;36:1703-19.

There have been some changes in SM diagnostic criteria. CD30 and any *KIT* mutation have been introduced as minor diagnostic criteria. Basal serum tryptase level >20 ng/mL is also a minor criterion.[55] This level is to be adjusted in patients of hereditary alpha-tryptasemia. Bone marrow mastocytosis is a new SM subtype marked by the absence of skin lesions and B-findings and a basal serum tryptase level <125 ng/mL. There have been some improvements in B (burden of disease) and C-findings (cytoreduction requiring), most important of which is that *KIT D816V* mutation with variant

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BOX 5 Mastocytosis types and subtypes.

Cutaneous mastocytosis:

- Urticaria pigmentosa/maculopapular cutaneous mastocytosis
- Monomorphic
- Polymorphic
- Diffuse cutaneous mastocytosis
- Cutaneous mastocytoma
- Isolated mastocytoma
- Multilocalized mastocytoma

Systemic mastocytosis:

- Bone marrow mastocytosis
- Indolent systemic mastocytosis
- Smoldering systemic mastocytosis
- Aggressive systemic mastocytosis
- Systemic mastocytosis with an associated hematologic neoplasm
- Mast cell leukemia

Mast cell sarcoma

Note: Well-differentiated systemic mastocytosis (WDSM) represents a morphologic variant that may occur in any SM type/subtype, including mast cell leukemia.

Source: Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022;36:1703-19.

allele frequency (VAF) ≥10% in bone marrow or peripheral blood leukocytes is now considered a B-finding.

Well-differentiated systemic mastocytosis (WDSM) is acknowledged as a morphological pattern that can be seen in any SM subtype, showing round, well-granulated mast cells widely infiltrating the marrow. In many such patients, *KIT 816* mutation is not found and the abnormal mast cells are positive for CD30 and negative for CD25 and CD2.[56]

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE GENE FUSIONS

These cancers cover extensive histologic types ranging from MPN, MDS, MDS/MPN, AML, and MPAL as well as B- or T-lymphoblastic leukemia/lymphoma (ALL). Till now, they included fusions of genes, such as *PDGFRA*, *PDGFRB,* and *FGFR1* with various partners. Now, a new category of MLN-TK with JAK2 rearrangement, involving *JAK2* fusion with genes other than *PCM1*, has been identified.[57,58] Rare cases of *FLT3* rearrangement have been seen and included in this category as well as MLN-TK with ETV6::ABL1 fusion.[59]

MLN-TK with other defined tyrosine kinase fusions includes all remaining genetic abnormalities involving tyrosine kinase genes which are very rare and thus very little is known about them **(Box 6)**.[60,61]

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BOX 6 **Genetic abnormalities defining myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions.**

- *PDGFRA* rearrangement
- *PDGFRB* rearrangement
- *FGFR1* rearrangement
- *JAK2* rearrangement
- *FLT3* rearrangement
- *ETV6::ABL1* fusion

Other defined tyrosine kinase fusions:

- *ETV6::FGFR2; ETV6::LYN; ETV6::NTRK3; RANBP2::ALK; BCR::RET; FGFR1OP::RET*

Source: Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022;36:1703-19.

GENETIC TUMOR SYNDROMES WITH PREDISPOSITION TO MYELOID NEOPLASIA

The new WHO classification recognizes five hematologic subtypes of FA based on blast percentage, *RAS*-pathway gene mutations and/or classic phenotype suggestive of a RASopathy.[62]

CONCLUSION

Understanding and unmasking biology and potential target sites is a process continuum. Focused efforts and innovative research is slowly but surely rewarding. We started in fifties with vincristine, methotrexate, 6-mercaptopurine with incorporation of radiotherapy and in 2023 we discuss where and how to incorporate biosimilars, CAR T cell, and other targeted therapies in pipeline. Focus of our discussion is now how to mitigate side effects and make these modalities patient friendly.

This chapter highlights and underscore recent advances in pediatric leukemia with a desired objective and goal to make it a confident success story with no neurocognitive sequelae.

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