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The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms

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The upcoming 5th edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours is part of an effort to hierarchically catalogue human cancers arising in various organ systems within a single relational database. This paper summarizes the new WHO classification scheme for myeloid and histiocytic/dendritic neoplasms and provides an overview of the principles and rationale underpinning changes from the prior edition. The definition and diagnosis of disease types continues to be based on multiple clinicopathologic parameters, but with refinement of diagnostic criteria and emphasis on therapeutically and/or prognostically actionable biomarkers. While a genetic basis for defining diseases is sought where possible, the classification strives to keep practical worldwide applicability in perspective. The result is an enhanced, contemporary, evidence-based classification of myeloid and histiocytic/dendritic neoplasms, rooted in molecular biology and an organizational structure that permits future scalability as new discoveries continue to inexorably inform future editions.

Leukemia (2022) 36:1703–1719; https://doi.org/10.1038/s41375-022-01613-1

INTRODUCTION

The World Health Organization (WHO) classification of tumours is an evidence-based classification of cancers occurring within various organ systems. It is a standard for diagnosis, research, cancer registries, and public health monitoring worldwide. For the first time since the inception of the classification over 60 years ago, the current series (5th edition) has been developed within a unified relational database framework that encompasses the entirety of human cancers. Tumours of each organ system and across volumes (blue books) are classified hierarchically within this novel framework along taxonomy principles and a set of non-negotiables that include process transparency, bibliographic rigor, and avoidance of bias [1, 2]. The development of the 5th edition is overseen by an editorial board that includes *standing members*—representatives from major medical and scientific organizations around the world—who oversee the entire series, in addition to *expert members* appointed for their leadership and contemporaneous expertise relevant to a particular volume [3]. The editorial board, in turn, identifies authors through an informed bibliometry process, with an emphasis on broad geographic representation and multidisciplinary expertise. By design, multidisciplinary author/editor groups (a total of 420 contributors) shared overlapping coverage of disease categories to ensure conceptual continuity and content harmonization. This approach reflects the ways in which the classification is meant to be implemented, with multidisciplinary input that emphasizes a holistic approach to patient management from diagnosis through disease monitoring.

The aim of this paper is to provide an overview of the new edition of the WHO classification for myeloid and histiocytic/dendritic tumours. The last edition of the haematolymphoid classification dates back to 2008 and was revised in 2017. An overview of the lymphoid tumours is provided in a companion manuscript [4].

The classification structure follows a lineage-based framework, flowing broadly from benign to malignant and branching down to category, family, type (disease/tumour), and subtype. Where possible, a triad of attributes was systematically applied and included: lineage + dominant clinical attribute + dominant

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Received: 1 May 2022 Accepted: 20 May 2022
Published online: 22 June 2022

biologic attribute. Lineage attribution rests on immunophenotyping with flow cytometry and/or immunohistochemistry. Dominant clinical attributes are general features of the untreated disease and include descriptors such as acute, chronic, cytopenia(s) (myelodysplasia) and cytosis(es) (myeloproliferation). Most biologic attributes include gene *fusions*, *rearrangements*, and *mutations*. Fusions are part of the nomenclature of types/subtypes when the identities of both implicated genes are required or often desirable criteria for diagnosis (e.g., *PML*::*RARA*). Rearrangements, a broad term that encompasses a range of structural genomic alterations leading to gene fusions, are part of the nomenclature of types/subtypes when there are multiple possible fusion partner genes of a biologically dominant gene (e.g., *KMT2A*). Of note, the use of the term rearrangements is maintained in the classification due to its wide usage across prior editions, although it is recognized that it is more appropriate for genomic modifications in genes consisting of various segments (e.g., immunoglobulin genes and T-cell receptor genes). A deliberate attempt is made to prioritize classifying tumour types based on *defining genetic abnormalities* where possible.

Emerging entities are listed as disease subtypes under a novel rubric of *other defined genetic alterations*. This is envisioned as a landing spot in the classification to incorporate new/rare entities whose recognition is increasing as high-throughput molecular diagnostic tools become more available. This approach replaces the assignment of provisional status to such entities. It is recognized that the diagnosis of such subtypes might not be feasible in all practice settings. A set of decision support guidelines was adopted to aid in determining what subtypes would qualify in this context; they include: (1) having distinct molecular or cytogenetic features driven by established oncogenic mechanisms; (2) not meeting subtype criteria under other tumour types with defining genetic abnormalities; (3) having distinct pathologic and clinical features, including - but not limited to - response to therapeutic interventions; and, (4) at least two quality peer-review publications by distinct investigator groups.

The application of this classification is predicated on integrating morphologic (cytology and histology), immunophenotypic, molecular and cytogenetic data. This is in line with previous editions, with expanded numbers of disease types and subtypes that are molecularly defined. It is hoped that the genetic underpinnings of the classification will prompt the provision of health resources to ensure that the necessary genetic testing platforms are available to peruse the full potential of the classification. Notwithstanding, the full published classification will include listing of essential diagnostic criteria that have the broadest possible applicability, particularly in limited resource settings. A further aid to broader applicability is the improved hierarchical structure of the classification, which permits reverting to family (class)-level definitions when detailed molecular genetic analyses may not be feasible; this approach is further elaborated on in the introduction of the blue book.

In line with the rest of the WHO 5th edition series, the classification of myeloid and histiocytic/dendritic neoplasms follows the Human Genome Organization Gene Nomenclature Committee recommendations, including the new designation of gene fusions using double colon marks (::) [5].

CLONAL HAEMATOPOIESIS

Clonal haematopoiesis (CH) refers broadly to the presence of a population of cells derived from a mutated multipotent stem/progenitor cell harbouring a selective growth advantage in the absence of unexplained cytopenias, haematological cancers, or other clonal disorders. The incidence of CH increases with age [6]. Substantial advances in understanding the molecular genetics and public health implications of CH took place since the last classification, including recognition of their association with increased overall mortality, cardiovascular diseases, and myeloid malignancies. More specific emerging associations, such as those characterizing the VEXAS (*v*acuoles, *E*1 enzyme, *X*-linked, *a*utoinflammatory, *s*omatic *UBA1* mutations) syndrome [7], represent manifestations of the interplay between inflammation and CH/myeloid neoplasia that are being gradually uncovered. Inclusion of CH in the classification represents a key inaugural effort to define and codify such myeloid precursor lesions.

Clonal haematopoiesis of indeterminate potential (CHIP) is defined in the classification as a term referring specifically to CH harbouring somatic mutations of myeloid malignancy-associated genes detected in the blood or bone marrow at a variant allele fraction (VAF) of ≥ 2% (≥4% for X-linked gene mutations in males) in individuals without a diagnosed haematologic disorder or unexplained cytopenia [8]. (Supplemental Data Table S1) The significance of variants detected at lower levels is unclear at present.

Clonal cytopenia of undetermined significance (CCUS) is defined as CHIP detected in the presence of one or more persistent cytopenias that are otherwise unexplained by haematologic or non-haematologic conditions and that do not meet diagnostic criteria for defined myeloid neoplasms. Cytopenia definitions are harmonized for CCUS, MDS, and MDS/MPN; they include Hb <13 g/dL in males and <12 g/dL in females for anaemia, absolute neutrophil count $<1.8 \times 10^9$/L for leukopenia, and platelets $<150 \times 10^9$/L for thrombocytopenia [9].

Summary Box:

- CH is recognized as a category of precursor myeloid disease state.
- CHIP and CCUS are formally defined.

MYELOPROLIFERATIVE NEOPLASMS

Myeloproliferative neoplasms (MPN) are listed in Table 1. The main types remain largely unchanged from the prior edition. Initial diagnostic evaluation of MPN continues to depend on close correlation between clinical features, molecular diagnostics, and usually morphologic evaluation of a trephine bone marrow biopsy. Most MPN patients are diagnosed in chronic phase (CP), which may progress into a blast phase (BP) associated with the accumulation of secondary cytogenetic and/or molecular aberrations.

Chronic myeloid leukaemia risk factors are refined, and accelerated phase is no longer required

Chronic myeloid leukaemia (CML) is defined by the *BCR*::*ABL1* fusion resulting from t(9;22)(q34;q11). The natural history of untreated CML before the introduction of targeted tyrosine kinase inhibitors (TKI) was biphasic or triphasic: an initial indolent CP followed by a blast phase (BP), with or without an intervening accelerated phase (AP). With TKI therapy and careful disease monitoring, the incidence of progression to advanced phase disease has decreased, and the 10-year overall survival rate for

Table 1. Myeloproliferative neoplasms.

Chronic myeloid leukaemia
Polycythaemia vera
Essential thrombocythaemia
Primary myelofibrosis
Chronic neutrophilic leukaemia
Chronic eosinophilic leukaemia
Juvenile myelomonocytic leukaemia
Myeloproliferative neoplasm, not otherwise specified

CML is 80–90% [10, 11]. The designation of AP has thus become less relevant, where resistance stemming from *ABL1* kinase mutations and/or additional cytogenetic abnormalities and the development of BP represent key disease attributes [12, 13]. Accordingly, AP is omitted in the current classification in favour of an emphasis on high risk features associated with CP progression and resistance to TKI. Criteria for BP include: (1) ≥20% myeloid blasts in the blood or bone marrow; or (2) the presence of an extramedullary proliferation of blasts; or (3) the presence of increased lymphoblasts in peripheral blood or bone marrow. The optimal cutoff for lymphoblasts and the significance of low-level B-lymphoblasts remain unclear and require additional studies.

Minor changes in diagnostic criteria for *BCR::ABL1*-negative myeloproliferative neoplasms

The classification retains an emphasis on distinguishing between polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF) using diagnostic criteria established in previous editions, with minor refinements. Distinction between these types is based on integrating peripheral blood findings with molecular data and bone marrow morphologic evaluation findings, as none of these parameters alone provide sufficient diagnostic specificity.

Major diagnostic criteria for the diagnosis of PV include elevated haemoglobin concentration and/or haematocrit, accompanied by trilineage hyperplasia (panmyelosis), with pleomorphic mature megakaryocytes in the bone marrow, and NM_004972: JAK2 p.V617F or *JAK2* exon 12 mutations. As the determination of increased red cell mass with ^{51}Cr-labeled red cells has become uncommon in routine clinical practice, it has been removed as a diagnostic criterion. The diagnostic criteria of ET are well-established and have not changed.

Primary myelofibrosis (PMF) is characterized by a proliferation of abnormal megakaryocytes and granulocytes in the bone marrow, which is associated in fibrotic stages with a polyclonal increase in fibroblasts that drive secondary reticulin and/or collagen marrow fibrosis, osteosclerosis, and extramedullary haematopoiesis. Recognizing prefibrotic PMF remains necessary to separate it not only from ET and PV but also from fibrotic PMF [14]. The importance of serial monitoring of bone marrow fibrosis and spleen size using reproducible and standardized criteria remain pertinent, especially for patients receiving JAK1/2 inhibitors. PV and ET progress to AP (10-19% blasts) and BP (≥20% blasts) in a minority of cases, but leukaemic transformation is more frequent in PMF, and leukaemia-free survival is shorter in fibrotic than prefibrotic PMF [15, 16].

While *JAK2*, *CALR*, and *MPL* mutations are considered driver events, mutations in other genes – particularly *TET2*, *ASXL1*, and *DNMT3A* – are found in over half of patients with MPN. Mutations affecting splicing regulators (*SRSF2, SF3B1, U2AF1, ZRSR2*) and other regulators of chromatin structure, epigenetic functions and cellular signaling (e.g., *EZH2, IDH1, IDH2, CBL, KRAS, NRAS, STAG2, TP53*) are less common. These additional mutations are more frequent in PMF and advanced disease compared to PV and ET, and some are known to correlate with a poorer prognostic risk (e.g., *EZH2, IDH1, IDH2, SRSF2, U2AF1*, and *ASXL1* mutations in PMF).

Chronic neutrophilic leukaemia (CNL) is a *BCR::ABL1*-negative MPN characterized by sustained peripheral blood neutrophilia (white blood cell count (WBC) ≥ 25×10^9/L, with ≥80% segmented neutrophils and bands), bone marrow hypercellularity due to neutrophilic granulocyte proliferation, and hepatosplenomegaly. *CSF3R* mutations are common in this disease and detected in >60% of cases [17, 18].

Chronic eosinophilic leukaemia (CEL) is a multi-system disorder characterized by a sustained *clonal* proliferation of morphologically abnormal eosinophils and eosinophil precursors resulting in persistent hypereosinophilia in blood and bone marrow [19–21]. Several changes to the diagnostic criteria of CEL are introduced: (1) the time interval required to define sustained hypereosinophilia is reduced from 6 months to 4 weeks; (2) addition of requirement for both clonality and abnormal bone marrow morphology (e.g., megakaryocytic or erythroid dysplasia); and, (3) elimination of increased blasts (≥2% in peripheral blood or 5-19% in bone marrow) as an alternative to clonality. These criteria improve the distinction between CEL and entities such as idiopathic hypereosinophilic syndrome and hypereosinophilia of unknown significance [22]. As the criteria of CEL and its place relative to other disorders with eosinophilia have become well characterized, the qualifier "not otherwise specified" is no longer needed and has been omitted from the name.

As in prior editions, MPN, not otherwise specified (MPN-NOS) is a designation that should be reserved for cases with clinical, laboratory, morphologic, and molecular features of MPN but lacking diagnostic criteria of any specific MPN type or with features that overlap across distinct MPN types.

Juvenile myelomonocytic leukaemia is recognized as a myeloproliferative neoplasm of early childhood with frequent association with germline pathogenic gene variants

Juvenile myelomonocytic leukaemia (JMML) is a haematopoietic stem cell-derived myeloproliferative neoplasm of early childhood. The pathogenetic mechanism in at least 90% of cases involves unchecked activation of the RAS pathway. A diagnosis of JMML can be made by combining clinical, laboratory, and molecular criteria. Updates to diagnostic criteria include: (1) exclusion of *KMT2A* rearrangements; (2) elimination of monosomy 7 as a cytogenetic criterion; and, (3) emphasizing the significance of diagnostic molecular studies, particularly those aimed at demonstrating RAS pathway activation. The genetic background of JMML plays a major role in risk stratification and therapeutic approaches, with cases initiated by somatic mutations involving *PTPN11* and germline pathogenic variants associated with neurofibromatosis type 1 being the most aggressive types, while some cases associated with pathogenic germline *CBL* variants undergoing occasionally spontaneous remission. The inclusion of JMML under MPN reflects its molecular pathogenesis and underscores the virtual absence of stigmata of bona fide myelodysplastic neoplasia in this disease.

Summary Box:

- CML phases consolidated into chronic and blast phases, with emphasis on risk features in chronic phase.
- Diagnostic criteria of CEL are updated, and the qualifier NOS is omitted.
- JMML is categorized under myeloproliferative neoplasms.

MASTOCYTOSIS

Mastocytosis comprises rare heterogeneous neoplasms characterized by an accumulation of abnormal mast cells in various organs or tissues, typically driven by constitutive activation of the KIT receptor. The pathology of mastocytosis is complex, and clinical features span a broad spectrum that may be modulated by the presence of comorbidities. Significant comorbidities include IgE-dependent allergies, vitamin D deficiency, and psychiatric, psychological or mental problems. The classification continues to recognize three disease types: systemic mastocytosis (SM), cutaneous mastocytosis (CM) and mast cell sarcoma (MCS) [23]. (Table 2)

A somatic point mutation in the *KIT* gene at codon 816 is detected in >90% of patients with SM. Other rare activating *KIT* alterations include mutations in the extracellular (e.g., deletion of codon 419 on exon 8 or A502_Y503dup in exon 9), transmembrane (e.g., NM_000222:KIT p.F522C), or juxtamembrane (e.g., NM_000222:KIT p.V560G) domains, detected in <1% of advanced

SM cases but enriched in cases of indolent SM. Most patients with advanced SM and NM_000222:*KIT* p.D816V have additional somatic mutations involving most frequently *TET2, SRSF2, ASXL1, RUNX1*, and *JAK2*. An associated haematologic (usually myeloid) neoplasm may be detected in these patients [24].

Diagnostic criteria for SM have been modified. Namely, expression of CD30 and the presence of any *KIT* mutation causing ligand-independent activation have been accepted as minor diagnostic criteria. Basal serum tryptase level >20 ng/ml, which should be adjusted in case of hereditary alpha-tryptasaemia, is a minor SM criterion [25]. In addition, bone marrow mastocytosis is now a separate subtype of SM characterized by absence of skin lesions and B-findings and a basal serum tryptase below 125 ng/ml. Classical B-findings ('burden of disease') and C-findings ('cytoreduction-requiring') have undergone minor refinements. Most notably, NM_000222:*KIT* p.D816V mutation with VAF ≥ 10% in bone marrow cells or peripheral blood leukocytes qualifies as a B-finding.

The classification recognizes well-differentiated systemic mastocytosis (WDSM) as a morphologic pattern that can occur in any SM subtype, characterized by round and well-granulated mast cells usually heavily infiltrating the bone marrow. In most patients with WDSM, *KIT* codon 816 mutation is not detected, and neoplastic mast cells are usually negative for CD25 and CD2 but positive for CD30 [26].

Table 2. 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 haematologic 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 leukaemia.

Summary Box:

- Diagnostic criteria for mastocytosis have been refined: CD30 and any *KIT* mutation are introduced as minor diagnostic criteria.
- Bone marrow mastocytosis is a new SM subtype.
- *KIT* D816V mutation with VAF ≥ 10% qualifies as a B-finding.

MYELODYSPLASTIC NEOPLASMS

New terminology and grouping framework

The classification introduces the term *myelodysplastic neoplasms* (abbreviated MDS) to replace myelodysplastic syndromes, underscoring their neoplastic nature and harmonizing terminology with MPN. These clonal haematopoietic neoplasms are defined by cytopenias and morphologic dysplasia. As indicated above, cytopenia definitions are adopted for consistency across CCUS, MDS, and MDS/MPN. Additionally, the recommended threshold for dysplasia is set at 10% for all lineages. MDS entities are now grouped as those having *defining genetic abnormalities* and those that are *morphologically defined*. (Table 3) It is posited that such reorganization enhances classification rigor by emphasizing genetically-defined disease types and ceding the prior emphasis on 'risk-based' grouping in the classification (based on blast percentage, ring sideroblasts, and number of lineages with dysplasia) in favour of more comprehensive risk-stratification

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)	<5% BM and <2% PB	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-bi*TP53*)	<20% BM and PB	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)	<5% BM and <2% PB		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

[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.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

schemes such as the Revised International Prognostic Scoring System for MDS (IPSS-R) [27]. An additional modification is a clarified terminology to distinguish between MDS with *low* blasts (MDS-LB) and MDS with *increased* blasts (MDS-IB), while retaining longstanding cutoffs.

MDS with defining genetic abnormalities

Myelodysplastic neoplasms with defining genetic abnormalities are grouped together and include: *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-bi*TP53*). The latter supersedes MDS-5q and MDS-*SF3B1*.

The diagnostic criteria of MDS-5q have not changed. While recognized as factors that may potentially alter the biology and/or prognosis of the disease, the presence of *SF3B1* or a *TP53* mutation (not multi-hit) does not per se override the diagnosis of MDS-5q.

Recent studies have identified MDS-*SF3B1* as a distinct disease type that includes over 90% of MDS with ≥5% ring sideroblasts [28]. The term *MDS with low blasts and ring sideroblasts* is retained as an acceptable alternative to be used for cases with wild-type *SF3B1* and ≥15% ring sideroblasts. This permits inclusion of rare MDS cases harbouring driver mutations in other RNA splicing components.

Pathogenic *TP53* alterations of any type (sequence variations, segmental deletions and copy neutral loss of heterozygosity) are detected in 7-11% of MDS [29–31]. Among these, about two-thirds of patients have multiple *TP53* hits (multi-hit), consistent with biallelic *TP53* alterations [29]. Biallelic *TP53* (bi*TP53*) alterations may consist of multiple mutations or mutation with concurrent deletion of the other allele. This "multi-hit" mutational status results in a neoplastic clone that lacks any residual wild-type p53 protein. Clinical detection of biallelic *TP53* alterations is based on sequencing analysis (covering at least exons 4 to 11) [29, 32], often coupled with a technique to detect copy number status, usually fluorescence in situ hybridization with a probe set specific for the *TP53* locus on 17p13.1 and/or array techniques (e.g., comparative genomic hybridization or single nucleotide polymorphism arrays) [33]. Loss of genetic material at the *TP53* locus may also be inferred by next-generation sequencing [29]. A *TP53* VAF ≥ 50% may be regarded as presumptive (not definitive) evidence of copy loss on the trans allele or copy neutral loss of heterozygosity when a constitutional *TP53* variant can be ruled out. When two or more *TP53* mutations are detected, they usually affect both alleles [29] and can be considered a multi-hit status. Over 90% of patients with MDS-bi*TP53* have complex, mostly very complex (>3), karyotype [29, 30] and thus are regarded as very high risk in IPSS-R [27]. Additional studies are needed to determine whether bi*TP53* status is per se AML-defining, a point for consideration in future editions. Notwithstanding, published data suggests that MDS-bi*TP53* may be regarded as AML-equivalent for therapeutic considerations [29, 30].

MDS, morphologically defined

Hypoplastic MDS (MDS-h) is listed as a distinct MDS type in this edition. Long recognized as having distinctive features, MDS-h is associated with a T-cell mediated immune attack on haematopoietic stem and progenitor cells, along with oligoclonal expansion of CD8 + cytotoxic T-cells overproducing IFNγ and/or TNFα. Several features overlap across the triad of MDS-h, paroxysmal nocturnal haemoglobinuria (PNH) and aplastic anaemia (AA), including an association with CH [34–36]. Many patients with MDS-h have sustainable responses to agents used in patients with AA (i.e., anti-thymocyte globulin, ATG). As such, an emphasis is placed on careful morphologic evaluation, typically requiring trephine biopsy evaluation in addition to evaluation of bone marrow smears and touch preparations, and detection of mutations and/or clonal cytogenetic abnormalities. Individuals with germline pathogenic variants in *GATA2*, *DDX41*, Fanconi anaemia (FA) or telomerase complex genes can have hypoplastic bone marrow and evolve to MDS and/or AML and do not respond to immunosuppressive treatment.

As the number of dysplastic lineages is usually dynamic and often represents clinical and phenotypic manifestation of clonal evolution – rather than per se defining a specific MDS type, the distinction between single lineage and multilineage dysplasia is now considered optional. The updated MDS classification scheme and the incorporation of CCUS in the classification obviates the need for "NOS" or "unclassifiable" attributes. Specifically, MDS, unclassifiable, which was present in the prior edition, is removed.

The boundary between MDS and AML is softened, but the 20% blast cutoff to define AML is retained

Reassessment of the bone marrow blast percentage defining the boundary of MDS-IB2 and AML has been advocated for several cogent reasons and in view of novel therapeutic approaches that show efficacy in patients currently classified as MDS or AML with 10-30% myeloid blasts [37–39]. Salient practical challenges underpinning arguments for such a reassessment include: (1) any blast-based cutoff is arbitrary and cannot reflect the biologic continuity naturally inherent in myeloid pathogenic mechanisms; (2) blast enumeration is subject to sampling variations/error and subjective evaluation; and, (3) no gold standard for blast enumeration exists, and orthogonal testing platforms can and often do produce discordant results. The pros and cons of merging MDS-IB2 with AML and adopting a 10% cutoff for what would be called MDS/AML were explored in multidisciplinary expert discussions and at editorial board meetings in the course of producing this classification. Lowering the blast cutoff to define AML was felt to suffer from the same challenges listed above and would merely replace one cutoff with another. Further, an arbitrary cutoff of 10% blasts to define AML (even if qualified as MDS/AML or AML/MDS) carries a risk of overtreatment. Accordingly, a balanced approach was adopted by eliminating blast cutoffs for most AML types with defining genetic alterations but retaining a 20% blast cutoff to delineate MDS from AML. Notwithstanding, there was broad agreement that MDS-IB2 may be regarded as AML-equivalent for therapeutic considerations and from a clinical trial design perspective when appropriate.

Childhood myelodysplastic neoplasms: Enhanced specificity of disease terminology introduced

Childhood MDS is a clonal haematopoietic stem cell neoplasm arising in children and adolescents (<18 years of age) leading to ineffective haematopoiesis, cytopenia(s), and risk of progression to AML. The annual incidence is 1-2 per million children, with 10-25% presenting with increased blasts. JMML, myeloid proliferations associated with Down syndrome, and MDS post cytotoxic therapy are excluded from this group and belong elsewhere in the classification. The qualifying term *childhood* MDS emphasizes that this category of myeloid neoplasms is biologically distinct from that seen in adults [40, 41], underscoring the need to further elucidate its pathogenesis which remains incompletely understood

Childhood MDS with low blasts (cMDS-LB) replaces the former term "refractory cytopenia of childhood (RCC)". It includes two subtypes: childhood MDS with low blasts, hypocellular; and, childhood MDS with low blasts, not otherwise specified (NOS). (Table 4) Exclusion of non-neoplastic causes of cytopenia such as infections, nutritional deficiencies, metabolic diseases, bone marrow failure syndromes (BMFS), and germline pathogenic variants remains an essential diagnostic prerequisite for childhood MDS with low blasts. Approximately 80% of cases show hypocellular bone marrow with features similar to severe aplastic anemia and other BMFS, requiring close morphologic examination to evaluate the distribution, maturation, and presence of dysplasia in haematopoietic lineages [42]. Some cytogenetic findings such

Table 4. Childhood myelodysplastic neoplasms (MDS).

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

BM bone marrow, *PB* peripheral blood.

as monosomy 7, 7q deletion, or complex karyotype are associated with an increased risk of progression to AML and typically treated with haematopoietic stem cell transplantation, while cases with normal karyotype or trisomy 8 can have an indolent course.

Childhood MDS with increased blasts (cMDS-IB) is defined as having ≥5% blasts in the bone marrow or ≥2% blasts in the peripheral blood. The genetic landscape of cMDS-IB and cMDS-LB is similar, and they both differ from MDS arising in adults. Acquired cytogenetic abnormalities and RAS-pathway mutations are more common in cMDS-IB compared to cMDS-LB [43, 44].

Summary Box:

- Myelodysplastic syndromes renamed myelodysplastic neoplasms (abbreviated MDS).
- MDS genetic types updated to include MDS-5q, MDS-*SF3B1* and MDS-bi*TP53*
- Hypoplastic MDS (MDS-h) is recognized as a distinct disease type.
- MDS with low blasts (MDS-LB) is a new term that enhances clarity.
- MDS with increased blasts (MDS-IB) is a new term that enhances clarity.
- Terminology of childhood MDS types is updated.

MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS

This category of myeloid neoplasms is defined by overlapping pathologic and molecular features of MDS and MPN, often manifesting clinically with various combinations of cytopenias and cytoses. The definition of cytopenias is the same as that for MDS. The classification includes major revisions in the diagnostic criteria of CMML and terminology changes for other MDS/MPN types. (Table 5)

Chronic myelomonocytic leukaemia diagnostic criteria, subtypes, and blast-based subgrouping criteria reflect diagnostic refinement and emphasize unifying characteristics

The prototype and most common MDS/MPN is chronic myelomonocytic leukaemia (CMML), which is characterized by sustained peripheral blood monocytosis and various combinations of somatic mutations involving epigenetic regulation, spliceosome, and signal transduction genes. Diagnostic criteria are revised to include prerequisite and supporting criteria. (Table 6) The first prerequisite criterion is persistent absolute (≥0.5 × 10^9/L) and relative (≥10%) peripheral blood monocytosis. Namely, the cutoff for absolute monocytosis is lowered from 1.0 ×10^9/L to 0.5 ×10^9/L to incorporate cases formerly referred to as oligomonocytic CMML [45–47]. To enhance diagnostic accuracy when absolute monocytosis is ≥0.5 ×10^9/L but <1.0 ×10^9/L, detection of one of more clonal cytogenetic or molecular abnormality and documentation of dysplasia in at least one lineage are required. Abnormal partitioning of peripheral blood monocyte subsets is introduced as a new supporting criterion [48, 49]. Additional studies are needed to determine the optimal approach to classifying individuals with unexplained clonal monocytosis [50] who do not fit the new diagnostic criteria of CMML.

Two disease subtypes with salient clinical and genetic features are now formally recognized based on WBC: *myelodysplastic* CMML (MD-CMML) (WBC < 13 × 10^9/L) and *myeloproliferative* CMML (MP-CMML) (WBC ≥ 13 × 10^9/L). MP-CMML is commonly associated with activating RAS pathway mutations and adverse clinical outcomes [51]. The blast-based subgroup of CMML-0 (<2% blasts in blood and <5% blasts in bone marrow) introduced in the previous edition has been eliminated in view of evidence that its addition provides no or limited prognostic significance [52, 53].

Table 5. Myelodysplastic/myeloproliferative neoplasms.

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

Atypical chronic myeloid leukaemia is renamed MDS/MPN with neutrophilia, and other terminology updates

Diagnostic criteria for other MDS/MPN types were largely unchanged. The term *MDS/MPN with neutrophilia* replaces the term atypical CML. This change underscores the MDS/MPN nature of the disease and avoids potential confusion with CML. MDS/MPN with ring sideroblasts and thrombocytosis is redefined based on *SF3B1* mutation and renamed *MDS/MPN with SF3B1 mutation and thrombocytosis*. The term MDS/MPN with ring sideroblasts and thrombocytosis has been retained as an acceptable term to be used for cases with wild-type *SF3B1* and ≥15% ring sideroblasts. MDS/MPN, unclassifiable is now termed *MDS/MPN, not otherwise specified*; this is in line with an intentional effort to remove the paradoxical qualifier "unclassifiable" from the entire classification.

Summary Box:

- CMML diagnostic criteria undergo major revisions, including lowering the cutoff for absolute monocytosis, adopting MD-CMML and MP-CMML subtypes, and eliminating CMML-0.
- Atypical chronic myeloid leukaemia renamed MDS/MPN with neutrophilia.
- MDS/MPN with ring sideroblasts and thrombocytosis redefined based on *SF3B1* mutation and renamed MDS/MPN with *SF3B1* mutation and thrombocytosis.

ACUTE MYELOID LEUKAEMIA

Enhanced grouping framework permitting scalable genetic classification and deemphasizing blast enumeration where relevant

The classification of AML is re-envisioned to emphasize major breakthroughs over the past few years in how this disease is understood and managed. Foremost is the separation of AML with defining genetic abnormalities from AML defined by differentiation. (Table 7) The latter eliminates the previously confusing use of the term AML NOS, under which types based on differentiation were listed. Another key change, as indicated above, is the elimination of the 20% blast requirement for AML types with defining genetic abnormalities (with the exception of AML with *BCR::ABL1* fusion and AML with *CEBPA* mutation). Removal of the blast cutoff requires correlation between morphologic findings and the molecular genetic studies to ensure that the defining abnormality is driving the disease pathology. This approach was deemed more appropriate than assigning another arbitrary lower bone marrow blast cutoff. A third component of the new structure is the introduction of a section on AML with *other defined genetic alterations*, a landing spot for new and/or uncommon AML subtypes that may (or may not) become defined types in future editions of the classification. As such, the overall AML classification structure continues to emphasize integration of clinical, molecular/genetic, and pathologic parameters and emphasis on clinicopathologic judgement.

Table 6. Diagnostic criteria of chronic myelomonocytic leukaemia.

Prerequisite criteria
1. Persistent absolute (≥0.5 × 10^9/L) and relative (≥10%) peripheral blood monocytosis.
2. Blasts constitute <20% of the cells in the peripheral blood and bone marrow.[a]
3. Not meeting diagnostic criteria of chronic myeloid leukaemia or other myeloproliferative neoplasms.[b]
4. Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with tyrosine kinase fusions.[c]
Supporting criteria
1. Dysplasia involving ≥1 myeloid lineages.[d]
2. Acquired clonal cytogenetic or molecular abnormality.
3. Abnormal partitioning of peripheral blood monocyte subsets.[e]
Requirements for diagnosis
- Pre-requisite 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 haematopoietic 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.

Table 7. Acute myeloid leukaemia.

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML*::*RARA* fusion
Acute myeloid leukaemia with *RUNX1*::*RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB*::*MYH11* fusion
Acute myeloid leukaemia with *DEK*::*NUP214* fusion
Acute myeloid leukaemia with *RBM15*::*MRTFA* fusion
Acute myeloid leukaemia with *BCR*::*ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia with *CEBPA* mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations
Acute myeloid leukaemia, defined by differentiation
Acute myeloid leukaemia with minimal differentiation
Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia

AML with defining genetic abnormalities

While the classification retains much of the established diagnostic criteria for AML with *PML*::*RARA*, AML with *RUNX1*::*RUNX1T1*, and AML with *CBF*::*MYH11*, increased recognition of the importance of highly sensitive measurable residual disease (MRD) evaluation techniques, and the impact of concurrent molecular alterations reflect factors that impact patient management and therapeutic decisions in current practice. Namely, prognostic factors have expanded from *KIT* mutations, which are still relevant, to include additional cytogenetic features and MRD status post induction. The diagnostic criteria of AML with *DEK*::*NUP214* and AML with *RBM15*::*MRTFA* (formerly *RBM15*::*MKL1*) have also remained largely unchanged.

AML with *BCR*::*ABL1* and AML with *CEBPA* mutation are the only disease types with a defined genetic abnormality that require at least 20% blasts for diagnosis. The blast cutoff requirement is needed for the former to avoid overlap with CML. Distinguishing AML with *BCR*::*ABL1* from initial myeloid blast phase of CML can be challenging, and additional evidence continues to be needed to better characterize this AML type. There is insufficient data to support any change in the blast cutoff criterion for AML with *CEBPA* mutation [54, 55].

Three AML types with characteristic rearrangements involving *KMT2A, MECOM*, and *NUP98* are recognized. A blast count under 20% is acceptable based on studies demonstrating that patients with <20% blasts (MDS) and any of these rearrangements have clinical features that resemble those with higher blast counts. It is important to note that rearrangements involving these three genes, particularly *NUP98*, may be cryptic on conventional karyotyping. *AML with KMT2A rearrangement* is the new term that replaces "AML with t(9;11)(p22;q23); *KMT2A-MLLT3*". More than 80 *KMT2A* fusion partners have been described, with *MLLT3, AFDN, ELL*, and *MLLT10* being most common. While not required, the identification of the fusion partner is desirable since it could provide prognostic information and may impact disease monitoring. Adult patients often present with high blast counts, usually with monocytic differentiation. In children particularly, AML with *KMT2A*::*MLLT3* and *KMT2A*::*MLLT10* show megakaryoblastic differentiation and/or low blast counts in bone marrow aspirate smears.

AML defined by mutations include AML with *NPM1* and AML with *CEBPA* mutation. AML with *NPM1* mutation can be diagnosed irrespective of the blast count, albeit again with emphasis on judicious clinicopathologic correlation. This approach aligns with data showing that cases previously classified as MDS or MDS/MPN with *NPM1* progress to AML in a short period of time. Similar data have emerged from patients with CH who acquire *NPM1* mutation. The definition of AML with *CEBPA* mutation has changed to include biallelic (biCEBPA) as well as single mutations located in the basic leucine zipper (bZIP) region of the gene (smbZIP-*CEBPA*). The favourable prognosis associated with smbZIP-*CEBPA* has been demonstrated in cohorts of children and adults up to 70 years old. *RUNX1* mutations in AML overlap with such a broad range of defining molecular features that it was determined to lack enough specificity to define a standalone AML type.

Table 8. Cytogenetic and molecular abnormalities defining acute myeloid leukaemia, myelodysplasia-related.

Defining cytogenetic abnormalities
Complex karyotype (≥3 abnormalities)
5q deletion or loss of 5q due to unbalanced translocation
Monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation
11q deletion
12p deletion or loss of 12p due to unbalanced translocation
Monosomy 13 or 13q deletion
17p deletion or loss of 17p due to unbalanced translocation
Isochromosome 17q
idic(X)(q13)
Defining somatic mutations
ASXL1
BCOR
EZH2
SF3B1
SRSF2
STAG2
U2AF1
ZRSR2

Several changes were introduced to the entity formerly designated AML with myelodysplasia-related changes, now called *AML, myelodysplasia-related* (AML-MR). This AML type is defined as a neoplasm with ≥20% blasts expressing a myeloid immunophenotype and harboring specific cytogenetic and molecular abnormalities associated with MDS, arising *de novo* or following a known history of MDS or MDS/MPN. Key changes include: (1) removal of morphology alone as a diagnostic premise to make a diagnosis of AML-MR; (2) update of defining cytogenetic criteria; and, (3) introduction of a mutation-based definition based on a set of 8 genes – *SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, STAG2*, > 95% of which are present specifically in AML arising post MDS or MDS/MPN [56, 57]. The presence of one or more cytogenetic or molecular abnormalities listed in Table 8 and/or history of MDS or MDS/MPN are required for diagnosing AML-MR.

AML with *other defined genetic alterations* represents a landing spot for new, often rare, emerging entities whose recognition is desirable to determine whether they might constitute distinct types in future editions. At present, subtypes under this heading include AML with rare genetic fusions.

AML defined by differentiation

This AML family includes cases that lack defining genetic abnormalities. (Table 9) It is anticipated that the number of such cases will diminish as discoveries provide novel genetic contexts for their classification. Notwithstanding, categorizing AML cases lacking defining genetic abnormalities based on differentiation offers a longstanding classification paradigm with practical, prognostic, and perhaps therapeutic implications.

The classification includes an updated comprehensive framework of differentiation markers and criteria, harmonized with those of mixed-phenotype acute leukaemia (MPAL) and early T-precursor lymphoblastic leukaemia/lymphoma (ETP-ALL) (see section below on acute leukaemia of ambiguous lineage). Indeed, the recent identification of *BCL11B* rearrangements in MPAL T/Myeloid, ETP-ALL, acute leukaemia of ambiguous lineage (ALAL) and a subset of AML with minimal differentiation suggests a biologic continuum across these entities, a finding with likely implications on future editions of the classification [58–61].

Acute erythroid leukaemia (AEL) (previously pure erythroid leukaemia, an acceptable related term in this edition) is a distinct AML type characterized by neoplastic proliferation of erythroid cells with features of maturation arrest and high prevalence of biallelic *TP53* alterations. Diagnostic criteria include erythroid predominance, usually ≥80% of bone marrow elements, of which ≥30% are proerythroblasts (or pronormoblasts). The occurrence of AEL cases in which nucleated erythroid cells constitute less than 80% of bone marrow cellularity is recognized; such cases share the same clinicopathologic features of other AEL [62, 63]. The central role that biallelic *TP53* mutations play in this aggressive AML type is underscored [64, 65]. The diagnosis of AEL supersedes AML-MR. *De novo* AEL and cases that arise following MDS or MDS/MPN share distinctive morphologic features, with prominent proerythroblast proliferation. Proerythroblast have been shown to play an important role in treatment resistance and poor prognosis in AML patients [66, 67].

Several molecular drivers can give rise to acute megakaryoblastic leukaemia (AMKL), which arises within three clinical groups: children with Down syndrome, children without Down syndrome, and adults. Immunophenotyping and detection of markers of megakaryocytic differentiation are required to make a diagnosis of AMKL and detect the newly described "RAM immunophenotype", which correlates with *CBFA2T3*::*GLIS2*, a subtype of *AML with other defined genetic alterations*.

Myeloid sarcoma

Myeloid sarcoma represents a unique tissue-based manifestation of AML or transformed MDS, MDS/MPN, or MPN. Cases of *de novo* myeloid sarcoma should be investigated comprehensively, including cytogenetic and molecular studies, for appropriate classification and planning therapy. Molecular alterations in myeloid sarcoma and concurrent bone marrow disease are concordant in ~70% of patients, suggesting that myeloid sarcoma may be derived from a common haematopoietic stem cell or precursor [68, 69]. Relevant gene mutations are detected in a subset of patients with morphologically normal-appearing bone marrow, suggesting low-level clonal myeloid disease or CH in the bone marrow [68, 70].

Summary Box:

- AML is arranged into two families: AML with *defining genetic abnormalities* and AML *defined by differentiation*. AML, NOS is no longer applicable.
- Most AML with defining genetic abnormalities may be diagnosed with <20% blasts.
- AML-MR replaces the former term AML "with myelodysplasia-related changes", and its diagnostic criteria are updated. AML transformation of MDS and MDS/MPN continues to be defined under AML-MR in view of the broader unifying biologic features.
- AML with rare fusions are incorporated as subtypes under AML with *other defined genetic alterations*.
- AML with somatic *RUNX1* mutation is not recognized as a distinct disease type due to lack of sufficient unifying characteristics.

SECONDARY MYELOID NEOPLASMS

A newly segregated category encompassing diseases that arise in the setting of certain known predisposing factors

Myeloid neoplasms that arise secondary to exposure to cytotoxic therapy or germline predisposition are grouped in this category. AML transformation of MPN is retained in the MPN category, while AML transformation of MDS and MDS/MPN is kept under AML-MR (see above). The framework of this disease category was redesigned with an eye towards two important areas: (1) providing a scalable structure for incorporating novel discoveries in the area of germline predisposition to myeloid neoplasia; (2) recognizing the dual importance of cataloguing myeloid neoplasms that arise following exposure to cytotoxic therapies for

Table 9. Differentiation markers and criteria for acute myeloid leukaemia (AML) types defined by differentiation.

Type	Diagnostic criteria*
AML with minimal differentiation	• Blasts are negative (<3%) for MPO and SBB by cytochemistry
	• Expression of two or more myeloid-associated antigens, such as CD13, CD33, and CD117
AML without maturation	• ≥3% blasts positive for MPO (by immunophenotyping or cytochemistry) or SBB and negative for NSE by cytochemistry
	• Maturing cells of the granulocytic lineage constitute <10% of the nucleated bone marrow cells
	• Expression of two or more myeloid-associated antigens, such as MPO, CD13, CD33, and CD117
AML with maturation	• ≥3% blasts positive for MPO (by immunophenotyping or cytochemistry) or SBB by cytochemistry
	• Maturing cells of the granulocytic lineage constitute ≥10% of the nucleated bone marrow cells
	• Monocyte lineage cells constitute < 20% of bone marrow cells
	• Expression of two or more myeloid-associated antigens, such as MPO, CD13, CD33, and CD117
Acute basophilic leukemia	• Blasts & immature/mature basophils with metachromasia on toluidine blue staining
	• Blasts are negative for cytochemical MPO, SBB, and NSE
	• No expression of strong CD117 equivalent (to exclude mast cell leukemia)
Acute myelomonocytic leukaemia	• ≥20% monocytes and their precursors
	• ≥20% maturing granulocytic cells
	• ≥3% of blasts positive for MPO (by immunophenotyping or cytochemistry)
Acute monocytic leukaemia	• ≥80% monocytes and/or their precursors (monoblasts and/or promonocytes)
	• <20% maturing granulocytic cells
	• Blasts and promonocytes expressing at least two monocytic markers including CD11c, CD14, CD36 and CD64, or NSE positivity on cytochemistry
Acute erythroid leukaemia	• ≥30% immature erythroid cells (proerythroblasts)
	• Bone marrow with erythroid predominance, usually ≥80% of cellularity
Acute megakaryoblastic leukaemia	• Blasts express at least one or more of the platelet glycoproteins: CD41 (glycoprotein IIb), CD61 (glycoprotein IIIa), or CD42b (glycoprotein Ib)[b]

*Shared diagnostic criteria include:
- ≥20% blasts in bone marrow and/or blood (except for acute erythroid leukaemia).
- Criteria for AML types with defined genetic alterations are not met.
- Criteria for mixed-phenotype acute leukaemia are not met (relevant for AML with minimal differentiation).
- Not fulfilling diagnostic criteria for myeloid neoplasm post cytotoxic therapy.
- No prior history of myeloproliferative neoplasm.

BM bone marrow, *MPO* myeloperoxidase, *NSE* nonspecific esterase, *PB* peripheral blood, *SBB* Sudan Black B.

clinical purposes as well as population health purposes. The latter factor is gaining increased recognition as cancer survival is prolonged and the incidence of late complications of therapy such as secondary myeloid neoplasia increases. An overarching principle in this context is the requirement to consider "post cytotoxic therapy" and "associated with germline [gene] variant" as disease attributes that should be added as qualifiers to relevant myeloid disease types whose criteria are fulfilled as defined elsewhere in the classification, e.g. *AML with KMT2A rearrangement post cytotoxic therapy* or *MDS with low blasts associated with germline RUNX1 variant*.

Myeloid neoplasms post cytotoxic therapy: introduction of more precise terminology and novel associations with new cytotoxic drug classes

As in previous editions, this category includes AML, MDS, and MDS/MPN arising in patients exposed to cytotoxic (DNA-damaging) therapy for an unrelated condition. The terminology and definitions of this disease category have been modified slightly to reflect an improved understanding of the risk that CH plays as a risk factor for myeloid neoplasia related particularly to the expansion of pre-existing clones secondary to selection pressures of cytotoxic therapy agents in an altered marrow environment [71]. Thus, the diagnosis of myeloid neoplasms post cytotoxic therapy (MN-pCT) entails fulfilment of criteria for a myeloid neoplasm in addition to a documented history of chemotherapy treatment or large-field radiation therapy for an unrelated neoplasm [72]. This would exclude CCUS, which by definition lacks sufficient support for morphologic dysplasia. Cases with a '*de novo* molecular signature' such as *NPM1* mutation and core-binding factor leukaemias should still be assigned to this category since the "*post cytotoxic therapy*" designation is based on the medical history, and the indication of the most specific diagnosis in the pathology report is recommended when possible. Exposure to PARP1 inhibitors is added as a qualifying criterion for MN-pCT, and methotrexate has been excluded. It is recommended that specification of the type of myeloid neoplasm is made when possible, with the appendix "post cytotoxic therapy" appended, e.g. CMML post cytotoxic therapy.

The majority of AML-pCT and MDS-pCT are associated with *TP53* mutations. The outcomes of such patients are generally worse with biallelic (multi-hit) *TP53* alterations, manifesting as ≥2 *TP53* mutations, or with concomitant 17p/*TP53* deletion or copy neutral LOH. Less frequent mutations involve genes such as *PPM1D* and DNA-damage response genes that may require additional work-up for germline predisposition.

Myeloid neoplasms associated with germline predisposition: A novel scalable model is introduced

Myeloid neoplasms associated with germline predisposition include AML, MDS, MPN, and MDS/MPN that arise in individuals with genetic conditions associated with increased risk of

Table 10. Subtypes of myeloid neoplasms associated with germline predisposition.

Myeloid neoplasms with germline predisposition without a pre-existing platelet disorder or organ dysfunction
• Germline *CEBPA* P/LP variant (CEBPA-associated familial AML)
• Germline *DDX41* P/LP variant[a]
• Germline *TP53* P/LP variant[a] (Li-Fraumeni syndrome)
Myeloid neoplasms with germline predisposition and pre-existing platelet disorder
• Germline *RUNX1* P/LP variant[a] (familial platelet disorder with associated myeloid malignancy, FPD-MM)
• Germline *ANKRD26* P/LP variant[a] (Thrombocytopenia 2)
• Germline *ETV6* P/LP variant[a] (Thrombocytopenia 5)
Myeloid neoplasms with germline predisposition and potential organ dysfunction
• Germline *GATA2* P/LP variant (GATA2-deficiency)
• Bone marrow failure syndromes
◦ Severe congenital neutropenia (SCN)
◦ Shwachman-Diamond syndrome (SDS)
◦ Fanconi anaemia (FA)
• Telomere biology disorders
• RASopathies (Neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan syndrome-like disorders[a,b])
• Down syndrome[a,b]
• Germline *SAMD9* P/LP variant (MIRAGE Syndrome)
• Germline *SAMD9L* P/LP variant (SAMD9L-related Ataxia Pancytopenia Syndrome)[c]
• Biallelic germline *BLM* P/LP variant (Bloom syndrome)

[a]Lymphoid neoplasms can also occur.
[b]See respective sections.
[c]Ataxia is not always present.
P pathogenic, *LP* likely pathogenic.

myeloid malignancies. Myeloid neoplasms arising in individuals with Fanconi anemia, Down syndrome, and RASopathies are discussed in separate dedicated sections. These diseases are now classified using a formulaic approach that couples the myeloid disease phenotype with the predisposing germline genotype, e.g., AML with germline pathogenic variants in *RUNX1*. The clinical manifestations of these diseases are grouped into three subtypes under which most germline predisposition conditions can be assigned. (Table 10) Genetic counseling and evaluation of family history is an expected component of the diagnostic evaluation of index patients. Myeloid proliferations associated with Down syndrome, typically associated with somatic exon 2 or 3 *GATA1* mutation, continue to encompass two clonal conditions that arise in children with constitutional trisomy 21: transient abnormal myelopoiesis (TAM), which is confined to the first 6 months of life and myeloid leukaemia of Down syndrome (ML-DS).

Summary Box:

- Myeloid neoplasms (MDS, MDS/MPN, and AML) *post cytotoxic therapy* (MN-pCT) require full diagnostic work up; the term replaces *therapy-related*.
- Exposure to PARP1 inhibitors is added as a qualifying criterion for MN-pCT.
- The diagnostic framework for myeloid neoplasm associated with germline predisposition is restructured along a scalable model that can accommodate future refinement and discoveries.

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE GENE FUSIONS

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK) are myeloid or lymphoid neoplasms driven by rearrangements involving genes encoding specific tyrosine kinases leading to fusion products in which the kinase domain is constitutively activated leading to cell signaling dysregulation that promotes proliferation and survival. (Table 11) These *BCR::ABL1*-negative diseases have long been recognized in view of their distinctive clinicopathologic features and sensitivity to TKI. They encompass a broad range of histologic types, including MPN, MDS, MDS/MPN, AML, and MPAL, as well as B- or T- lymphoblastic leukaemia/lymphoma (ALL). Extramedullary disease is common. While eosinophilia is a common and salient feature, it may be absent in some cases. From a diagnostic hierarchy standpoint, the diagnosis of MLN-TK supersedes other myeloid and lymphoid types, as well as SM. In some instances, defining genetic abnormalities of MLN-TK are acquired during course of a myeloid neoplasm such as MDS or MDS/MPN or at the time of MPN BP transformation. MLN-TK must be excluded before a diagnosis of CEL is rendered.

The majority of MLN-TK cases associated with *PDGFRA* rearrangements have cytogenetically cryptic deletion of 4q12 resulting in *FIP1L1::PDGFRA*, but *PDGFRA* fusions involving other partners are also identified. Cases with *PDGFRB* rearrangement result most commonly from t(5;12)(q32;p13.2) leading to *ETV6::PDGFRB*; however, more than 30 other partners have been identified. Cases with *FGFR1* rearrangement may manifest as chronic myeloid neoplasms or blast-phase disease of B-cell, T-cell, myeloid or mixed-phenotype origin, typically with associated eosinophilia. The characteristic cytogenetic feature is an aberration of chromosome 8p11. Detection of *JAK2* rearrangements leading to fusion products with genes other than *PCM1* have been recognized, supporting MLN-TK with *JAK2* rearrangement as a distinct type [73, 74]. Cases with *FLT3* fusion genes are particularly rare and result from rearrangements involving chromosome 13q12.2. They manifest as myeloid sarcoma with MPN features in the bone marrow or T-ALL with associated eosinophilia, but disease features and phenotypic presentation may be variable and diverse. MLN-TK with *ETV6::ABL1* should be separated from B-ALL with *ETV6::ABL1* [75].

The natural history of MLN-TK with *PDGFRA* or *PDGFRB* has been dramatically altered by TKI therapy, particularly imatinib. In contrast, patients with *FGFR1*, *JAK2* and *FLT3* fusions and *ETV6::ABL1* have more variable sensitivity to available newer generation TKIs [73, 76]; in most cases, long-term disease-free survival may only be achievable with allogeneic haematopoietic stem cell transplantation.

Other less common defined genetic alterations involving tyrosine kinase genes have also been discovered, and these are listed as MLN-TK subtypes under *MLN-TK with other defined tyrosine kinase fusions* until further data is accrued [77, 78].

Summary Box:

- Family renamed myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK).
- Recognition of novel types with *JAK2* rearrangements, *FLT3* rearrangements, and *ETV6::ABL1* fusion.
- New scalable genetic framework introduced under MLN-TK with *other* defined tyrosine kinase fusions.

ACUTE LEUKAEMIAS OF MIXED OR AMBIGUOUS LINEAGE

Acute leukemia of ambiguous lineage (ALAL) and mixed-phenotype acute leukaemia (MPAL) are grouped under a single category in view of their overlapping clinical and

Table 11. 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

immunophenotypic features, which in recent studies have been shown to also share common molecular pathogenic mechanisms. Here too, a framework for a molecular classification is laid by separating ALAL/MPAL with defining genetic abnormalities from those that are defined based on immunophenotyping only. (Table 12)

Two new subtypes of ALAL with defining genetic alterations are added. The first subtype is MPAL with *ZNF384* rearrangement, which commonly has a B/myeloid immunophenotype and is identified in ~50% of pediatric B/myeloid MPAL with fusion partners including *TCF3*, *EP300*, *TAF15*, and *CREBBP*. *ZNF384*-rearranged B/myeloid MPAL and B-ALL have similar transcriptional profile, suggesting a biological continuum [79]. The other subtype is ALAL with *BCL11B* rearrangement, which has a more heterogenous immunophenotype - identified in acute undifferentiated leukaemia (AUL) and ~20-30% of T/myeloid MPAL. *BCL11B* rearrangement is also identified in AML with minimal differentiation or without maturation and ~20-30% of ETP-ALL. [59–61, 80] These different types of acute leukaemias with stem cell, myeloid, and T-ALL features having *BCL11B* rearrangement in common suggests a biological continuum. Other genomic findings such as *PHF6* mutations and *PICALM::MLLT10* fusions are also enriched in MPAL, but more studies are needed.

The assignment of lineage by immunophenotyping is dependent on the strength of association between each antigen and the lineage being assessed. As a general principle, the closer the expression of an antigen is to either the intensity and/or pattern of expression seen on the most similar normal population, the more likely it reflects commitment to that lineage. For instance, variable myeloperoxidase expression with an intensity and pattern similar to that seen in early myeloid maturation is more strongly associated with myeloid lineage than uniform dim myeloperoxidase expression. In addition, demonstration of a coordinated pattern of expression of multiple antigens from the same lineage further improves the specificity of those antigens for lineage assignment, e.g. combined expression of CD19, CD22, and CD10 is more strongly associated with B lineage than each antigen individually. Given these principles, the immunophenotypic criteria to be used for lineage assignment in cases where a single lineage is not evident are revised. (Table 13)

Assessment of myeloperoxidase expression by cytochemistry and/or flow cytometry immunophenotyping plays a key role intersecting AML with minimal differentiation, T/myeloid MPAL, and ETP-ALL. Various groups have proposed flow cytometry thresholds for positive myeloperoxidase expression in acute leukaemia, ranging from 3 to 28% of blasts [81–83]. The 3% cutoff for myeloperoxidase, historically used for cytochemistry, was determined to have high sensitivity but poor specificity for general lineage assignment in acute leukaemia by flow cytometry [82, 83]. A threshold of >10% for myeloperoxidase positivity seems to improve specificity [81], but no consensus cutoff has been established.

Summary Box:

- Acute leukaemias of mixed or ambiguous lineage are arranged into two families: ALAL with *defining genetic abnormalities* and ALAL, *immunophenotypically defined*.
- Novel genetic findings are listed as subtypes under ALAL *with other defined genetic alterations* as additional data accrues.
- Lineage assignment criteria for MPAL are refined to emphasize principles of intensity and pattern.

HISTIOCYTIC/DENDRITIC CELL NEOPLASMS

These neoplasms are positioned in the classification after myeloid neoplasms in recognition of their derivation from common myeloid progenitors that give rise to cells of the monocytic/histiocytic/dendritic lineages. (Table 14) Key changes in the current edition of the classification include: (1) inclusion of clonal plasmacytoid dendritic cell (pDC) diseases in this category; (2) moving follicular dendritic cell sarcoma and fibroblastic reticular cell tumor to a separate category; and, (3) addition of Rosai-Dorfman disease (RDD) and ALK-positive histiocytosis as disease types. Indeed, neoplasms that arise from lymphoid stromal cells such as follicular dendritic cell sarcoma and fibroblastic reticular cell tumor are now appropriately classified under the new chapter of "stroma-derived neoplasms of lymphoid tissues" as detailed in the companion manuscript [4].

Plasmacytoid dendritic cell neoplasms: recognition of clonal proliferations detected in association with myeloid neoplasms and refinement/update of the diagnostic criteria for blastic plasmacytoid dendritic cell neoplasm

Mature plasmacytoid dendritic cell proliferation (MPDCP) associated with myeloid neoplasm reflects recent data showing that these represent clonal proliferation of pDCs with low grade morphology identified in the context of a defined myeloid neoplasm. Clonal MPDCP cells accumulate in the bone marrow of patients with myeloproliferative CMML harbouring activating RAS pathway mutations [84]. Patients with AML can have clonally expanded pDCs (pDC-AML), which share the same mutational landscape as $CD34^+$ blasts, and frequently arise in association with *RUNX1* mutations [85, 86]. It is unknown whether the pathogenetic mechanisms leading to MPDCP in association with MDS or MDS/MPN and with AML are the same. The framework for diagnosing blastic plasmacytoid dendritic cell neoplasm remains largely the same, with emphasis on immunophenotypic diagnostic criteria. (Table 15)

Dendritic and histiocytic neoplasms: Rosai-Dorfman disease and ALK-positive histiocytosis are new entities in the classification

Much has been learned about the molecular genetics of histiocytoses/histiocytic neoplasms in recent years. These neoplasms, in particular Langerhans cell histiocytosis/sarcoma, Erdheim-Chester disease, juvenile xanthogranuloma, RDD and histiocytic sarcoma, commonly show mutations in genes of the MAPK pathway, such as *BRAF, ARAF, MAP2K1, NRAS* and *KRAS*, albeit with highly variable frequencies, indicating a unifying genetic landscape for diverse histiocytoses and histiocytic neoplasms. ALK-positive histiocytosis furthermore converges on the MAPK pathway, which is one of the signaling pathways mediating ALK activation [87, 88]. Insights on genetic alterations have significant treatment implications, because of availability of highly effective therapy targeting components of the activated signaling pathway, such as BRAF and MEK inhibitors [88–92].

For RDD, the distinctive clinicopathologic features with accumulation of characteristic S100-positive large histiocytes showing emperipolesis, coupled with frequent gain-of-function mutations in genes of the MAPK pathway indicating a neoplastic

process, provides a rationale for this inclusion and offers opportunities for targeted therapy [92–95].

ALK-positive histiocytosis, which shows a broad clinicopathologic spectrum unified by the presence of ALK gene translocation (most commonly *KIF5B*::*ALK*) and remarkable response to ALK-inhibitor therapy, has been better characterized in recent studies [88, 96]. The multisystem systemic form that typically occurs in infants, with involvement of liver, spleen and/or bone marrow, runs a protracted course but often resolves slowly, either spontaneously or with chemotherapy. Other multisystem and single-system cases occur in any age group, with involvement of two or more organs or one organ alone, respectively, most commonly central/peripheral nervous system and skin; the disease has a favourable outcome with systemic and/or surgical therapy [88, 97]. The histiocytes in ALK-positive histiocytosis can assume variable appearances including large oval cells, foamy cells and spindle cells, some with multinucleation (including Touton giant cells) or emperipolesis. That is, morphology is not entirely diagnostic, and overlaps extensively with that of juvenile xanthogranuloma and rarely RDD. Thus, it is recommended that ALK immunostaining be performed for histiocytic proliferations not conforming to defined entities, to screen for possible ALK-positive histiocytosis.

In most circumstances, classification of a dendritic cell/macrophage neoplasm as Langerhans cell histiocytosis/sarcoma, indeterminate dendritic cell tumor, interdigitating dendritic cell sarcoma or histiocytic sarcoma is straightforward. Nonetheless, there are rare cases that show overlap or hybrid features, defying precise classification [98, 99].

Among histiocytic neoplasms, a subset of cases occurs in association with or follow a preceding lymphoma/leukaemia, most commonly follicular lymphoma, chronic lymphocytic leukaemia and T- or B-ALL [100]. Since these histiocytic neoplasms usually exhibit the same clonal markers and/or hallmark genetic changes as the associated lymphoma/leukaemia, a "transdifferentiation" mechanism has been proposed to explain the phenomenon [99–101]. Furthermore, the histiocytic neoplasm and associated lymphoma/leukaemia often show additional genetic alterations exclusive to each component, suggesting that divergent differentiation or transdifferentiation occurs from a common lymphoid progenitor clone [100, 102, 103]. Histiocytoses are also sometimes associated with myeloproliferative neoplasms [104], sharing mutations with $CD34^+$ myeloid progenitors [105], and with CH [106].

Table 12. Acute leukaemias of ambiguous lineage.

Acute leukaemia of ambiguous lineage with defining genetic abnormalities
Mixed-phenotype acute leukaemia with *BCR*::*ABL1* fusion
Mixed-phenotype acute leukaemia with *KMT2A* rearrangement
Acute leukaemia of ambiguous lineage with other defined genetic alterations
Mixed-phenotype acute leukaemia with *ZNF384* rearrangement
Acute leukaemia of ambiguous lineage with *BCL11B* rearrangement
Acute leukaemia of ambiguous lineage, immunophenotypically defined
Mixed-phenotype acute leukaemia, B/myeloid
Mixed-phenotype acute leukaemia, T/myeloid
Mixed-phenotype acute leukaemia, rare types
Acute leukaemia of ambiguous lineage, not otherwise specified
Acute undifferentiated leukaemia

Summary Box:

- Histiocytic/dendritic cell neoplasms are regrouped and positioned to follow myeloid neoplasms in the classification scheme in view of their close ontogenic derivation.
- Mature pDC proliferation is redefined with an emphasis on recent data demonstrating shared clonality with underlying myeloid neoplasms. This framework is bound to evolve in future editions.
- Diagnostic criteria of BPDCN are refined.
- ALK-positive histiocytosis is introduced as a new entity.

GENETIC TUMOR SYNDROMES WITH PREDISPOSITION TO MYELOID NEOPLASIA

Fanconi anaemia is a heterogeneous disorder caused by germline variants in the BRCA-Fanconi DNA repair pathway (≥21 genes) resulting in chromosomal breakage and hypersensitivity to crosslinking agents used for diagnosis. Clinical features include congenital anomalies, bone marrow failure, and cancer predisposition [107]. The new classification distinguishes 5 haematologic categories depending on blast percentage,

Table 13. Lineage assignment criteria for mixed-phenotype acute leukaemia.

	Criterion
B lineage	
CD19 strong[a]	1 or more also strongly expressed: CD10, CD22, or CD79a[c]
or,	
CD19 weak[b]	2 or more also strongly expressed: CD10, CD22, or CD79a[c]
T lineage	
CD3 (cytoplasmic or surface)[d]	Intensity in part exceeds 50% of mature T-cells level by flow cytometry or, Immunocytochemistry positive with non-zeta chain reagent
Myeloid lineage	
Myeloperoxidase	Intensity in part exceeds 50% of mature neutrophil level
or,	
Monocytic differentiation	2 or more expressed: Non-specific esterase, CD11c, CD14, CD64 or lysozyme

[a]CD19 intensity in part exceeds 50% of normal B cell progenitor by flow cytometry.
[b]CD19 intensity does not exceed 50% of normal B cell progenitor by flow cytometry.
[c]Provided T lineage not under consideration, otherwise cannot use CD79a.
[d]Using anti-CD3 epsilon chain antibody.

Table 14. Dendritic cell and histiocytic neoplasms.

Plasmacytoid dendritic cell neoplasms
Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm
Blastic plasmacytoid dendritic cell neoplasm
Langerhans cell and other dendritic cell neoplasms
Langerhans cells neoplasms
Langerhans cell histiocytosis
Langerhans cell sarcoma
Other dendritic cell neoplasms
Indeterminate dendritic cell tumour
Interdigitating dendritic cell sarcoma
Histiocytic neoplasms
Juvenile xanthogranuloma
Erdheim-Chester disease
Rosai-Dorfman disease
ALK-positive histiocytosis
Histiocytic sarcoma

Table 15. Immunophenotypic diagnostic criteria of blastic plasmacytoid dendritic cell neoplasm.

Expected positive expression:
CD123*
TCF4*
TCL1*
CD303 *
CD304*
CD4
CD56
Expected negative markers:
CD3
CD14
CD19
CD34
Lysozyme
Myeloperoxidase
Immunophenotypic diagnostic criteria:
-Expression of CD123 and one other pDC marker(*) in addition to CD4 and/or CD56.
or,
-Expression of any three pDC markers and absent expression of all expected negative markers.

cytopenia and chromosomal abnormalities [108]. Dysgranulopoiesis and dysmegakaryopoiesis are histologic indicators of progression [109]. Allogenic haematopoietic stem cell transplantation is efficacious.

The term RASopathies encompasses a diverse group of complex, multi-system disorders associated with variants in genes involved in the RAS mitogen-activating protein kinase (MAPK) pathway. Myeloid neoplasms in RASopathies involve MAPK hyperactivation, leading to myeloid cell proliferation [110]. Genomic analysis of *NF1*, *NRAS*, *KRAS*, *PTPN11*, and *CBL* from myeloid neoplasms of patients suspected of having a RASopathy is important and aids in the diagnosis of JMML in the majority of cases [111, 112]. Diagnostic criteria include pathogenic variants in genes associated with the RAS pathway and/or classic phenotype suggestive of a RASopathy [113].

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ACKNOWLEDGEMENTS

We thank the leadership and staff of the International Agency for Research on Cancer (IARC), Lyon, France, especially Dr. Ian Cree and Ms. Asiedua Asante, for their tireless efforts.

The following colleagues are acknowledged for their expert contributions as authors in the WHO Classification of Haematolymphoid Tumours blue book on myeloid and histiocytic/dendritic cell topics:

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FUNDING

Open Access funding enabled and organized by Projekt DEAL.

COMPETING INTERESTS

All authors underwent IARC clearance for potential conflicts of interest regarding this work.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41375-022-01613-1.

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- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Myelodysplastic Syndromes

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Richard M. Stone, MD, Panel Vice Chair, scientific advisor for AbbVie Inc., Argos Therapeutics, Boston Scientific Corporation, CTI BioPharm Corp., Genentech, Inc., Janssen Pharmaceutica Products, LP, Jazz Pharmaceuticals Inc., Novartis Pharmaceuticals Corporation, and Syros Pharmaceuticals.

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This activity is supported by educational grants from AstraZeneca; BeiGene; Exact Sciences; Gilead Sciences, Inc.; GlaxoSmithKline; Lantheus Medical Imaging Inc.; Novartis; Pharmacyclics LLC, an AbbVie Company and Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC; and Taiho Oncology, Inc. This activity is supported by an independent educational grant from Astellas. This activity is supported by an education grant from Astellas and Seagen Inc. This activity is supported by a medical education grant from Karyopharm® Therapeutics. This activity is supported through an Independent Medical Education grant from Merck & Co., Inc.

Myelodysplastic Syndromes, Version 3.2022

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Myelodysplastic Syndromes (MDS) provide recommendations for the evaluation, diagnosis, and management of patients with MDS based on a review of clinical evidence that has led to important advances in treatment or has yielded new information on biologic factors that may have prognostic significance in MDS. The multidisciplinary panel of MDS experts meets on an annual basis to update the recommendations. These NCCN Guidelines Insights focus on some of the updates for the 2022 version of the NCCN Guidelines, which include treatment recommendations both for lower-risk and higher-risk MDS, emerging therapies, supportive care recommendations, and genetic familial high-risk assessment for hereditary myeloid malignancy predisposition syndromes.

J Natl Compr Canc Netw 2022;20(2):106–117
doi: 10.6004/jnccn.2022.0009

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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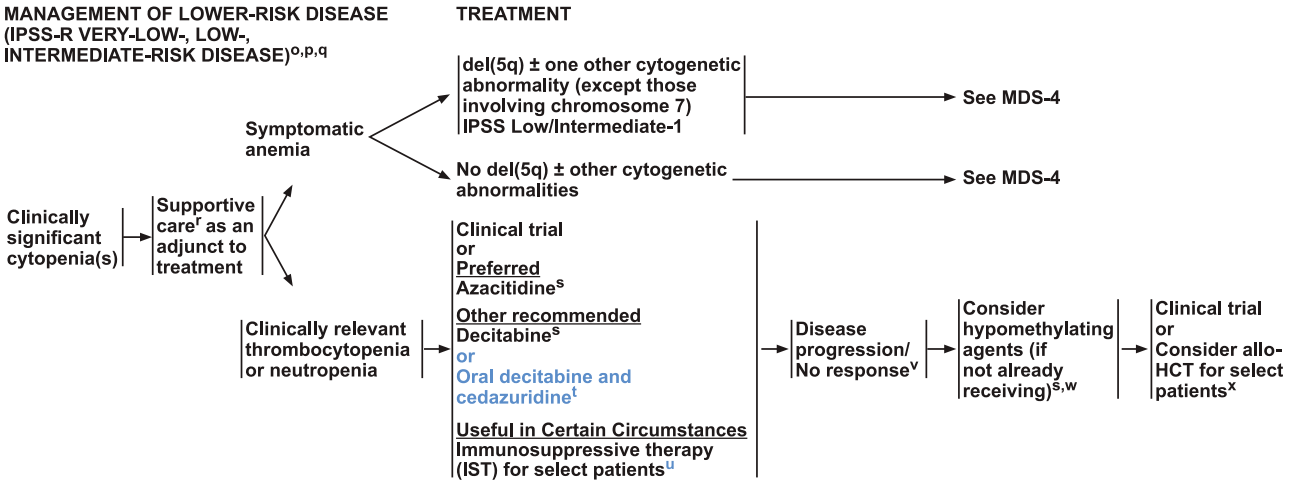


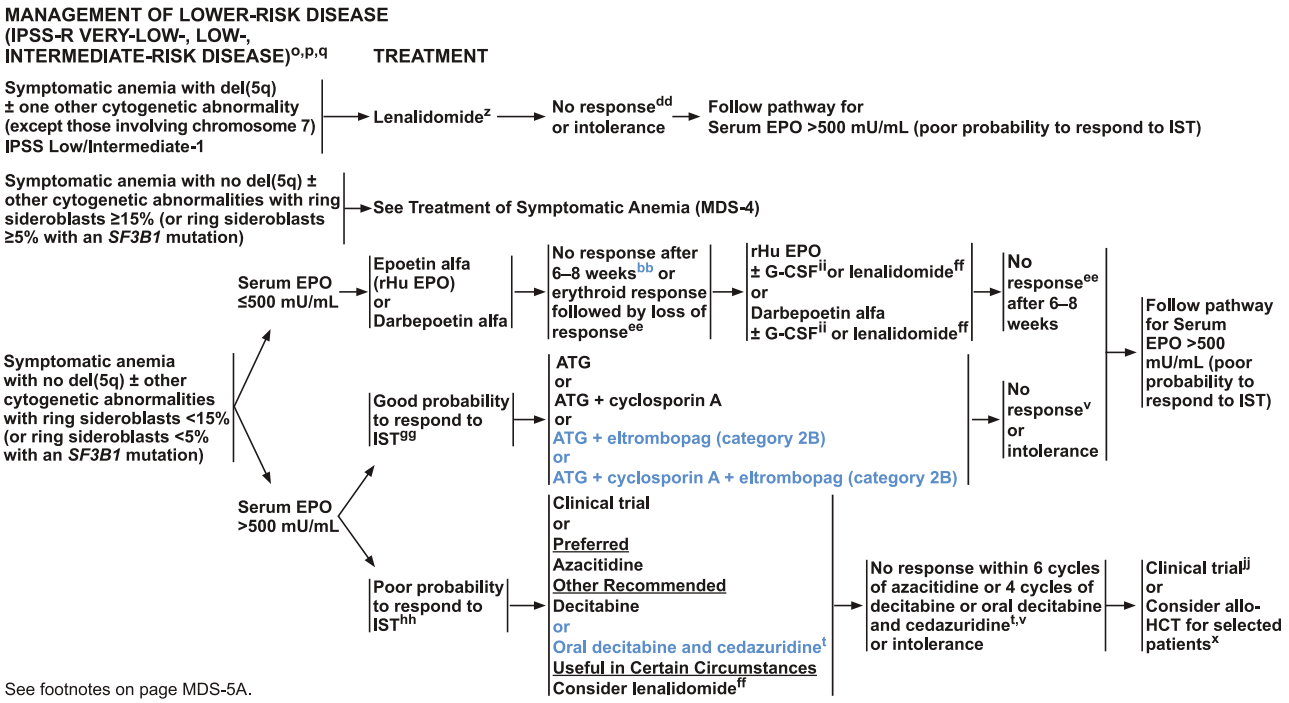
[o] Presence of comorbidities should also be considered for evaluation of prognosis (See Comorbidity Indices in the Discussion).
[p] Given its more accurate risk stratification, the IPSS-R categorization is preferred although the other systems also have good value. IPSS-R Intermediate patients may be managed as lower risk if their score is ≤3.5 vs. higher risk if score is >3.5. Pfeilstöcker M, et al. Blood 2016;128:902-910.
[q] If the disease is initially managed as lower risk but fails to respond, move to higher risk management strategies.
[r] See Supportive Care (MDS-7 and MDS-8).
[s] Some studies have demonstrated clinical benefit with low doses of azacitidine or decitabine for lower-risk MDS. Jabbour E, et al. Blood 2017;130:1514-1522.
[t] Oral decitabine and cedazuridine (DEC-C) could be a substitution for intravenous decitabine in patients with IPSS Intermediate-1 and above. (Garcia-Manero G, et al. Blood 2020;136:674-683).
[u] Patients generally ≤60 y and with ≤5% marrow blasts, or those with hypocellular marrows, PNH clone positivity, or STAT-3 mutant cytotoxic T-cell clones. IST includes equine ATG ± cyclosporin A ± eltrombopag. Additionally, for severe thrombocytopenia, eltrombopag alone could be considered.
[v] Response should be evaluated based on IWG criteria: Cheson BD, et al. Blood 2006;108:419-425. Failure would be considered if no response within 3–6 mo.
[w] For patients with severe or refractory thrombocytopenia, eltrombopag or romiplostim can be considered. Oliva EN, et al. Lancet Hematol 2017;4:e127-e136. Fenaux P, et al. Br J Haematol 2017;178:906-913. See Discussion.
[x] IPSS Intermediate-1, IPSS-R Intermediate, and WPSS Intermediate patients with severe cytopenias would also be considered candidates for HCT. Matched sibling, unrelated donor, or alternative (haploidentical or cord blood when appropriate) donor, including standard and reduced-intensity preparative approaches, may be considered.

MDS-3

Overview

Myelodysplastic syndromes (MDS) encompass a group of myeloid clonal hemopathies with a relatively heterogenous spectrum of presentation. Diagnosis and disease stratification are based on multiple factors, which may include clinical data, morphology of peripheral blood and bone marrow, fluorescence in situ hybridization, cytogenetics, flow cytometry, and next-generation sequencing myeloid mutation studies. The major clinical problems resulting from these disorders are morbidities caused by cytopenias and the potential for MDS to evolve into acute myeloid leukemia (AML). In addition, there are complications that may arise from chronic transfusions, treatment toxicity, and in some cases, secondary phenomena such as systemic inflammatory conditions.[1] The incidence rate of MDS is approximately 4.5 per 100,000 people per year in the general population.[2] MDS is rare among children, adolescents, and young adults. Accounting for 1.6% of patients diagnosed with MDS, individuals aged <40 years have an incidence of 0.1 per 100,000 people per year. However, this incidence increases to 26.9 per 100,000 for those between age 70 and 79 years, and to 55.4 per 100,000 for those aged ≥80 years.[2] Management of MDS is complicated by the generally advanced age of patients (median age, 77 years),[3] the nonhematologic comorbidities commonly seen in this cohort, and the relative inability of older patients to tolerate certain intensive forms of therapy. Upon disease progression to AML, these patients experience lower response rates to standard therapy compared with patients with de novo AML.[4]

The MDS panel has proposed stratifying patients with clinically significant cytopenia(s) into 2 major risk groups: (1) patients with lower-risk MDS (ie, international prognostic scoring system [IPSS] low, intermediate-1 [int-1]; revised IPSS [IPSS-R] very low, low, intermediate; WHO prognostic scoring system [WPSS] very low, low, intermediate); and (2) patients with higher-risk MDS (ie, IPSS int-2, high; IPSS-R intermediate, high, very high; WPSS high, very high). Patients with IPSS-R intermediate risk may be managed as lower risk if their score is ≤3.5 versus higher risk if their score is >3.5.[5] In addition, factors such as patient age, performance status, and presence of comorbidities have a major influence on the patient's ability to tolerate certain intensive treatments, and play a major role in selecting the optimal management strategy.



See footnotes on page MDS-5A.

z Recommended initial dose is: 10 mg/day for 21 out of 28 days or 28 days monthly for 2–4 months to assess response (See Discussion). Alternative option to lenalidomide may include an initial trial of ESAs in patients with serum EPO ≤500 mU/mL. Use caution for patients with low platelet and neutrophil counts; consider modifying lenalidomide dose. Sekeres MA, et al. J Clin Oncol 2008;26:5943-5949. Patients with monosomy 7 are an exception and should be treated in the higher prognostic risk category (see MDS-6).

MDS-5

Management of Lower-Risk MDS

During the annual meeting to update the NCCN Guidelines for MDS in 2022, the panel revisited the recommendation for oral decitabine and cedazuridine, which was previously included as a footnote, and agreed to add this recommendation directly in the algorithm (see MDS-3 and MDS-5, page 108 and above, respectively). As the clinical study documenting bioequivalence for this combination enrolled patients with IPSS int-1 and above, the panel decided to specify the prognostic risk category in a footnote: "Oral decitabine and cedazuridine could be a substitution for intravenous decitabine in patients with IPSS int-1 and above" (see MDS-3 and MDS-5A, pages 108 and 110, respectively).[6]

Furthermore, the panel discussed the addition of eltrombopag to immunosuppressive therapy (IST) for patients with lower-risk MDS, and voted to modify a footnote (see MDS-3, page 108). In the setting of clinically relevant thrombocytopenia or neutropenia, IST is recommended as an option that is useful in certain circumstances for select patients (generally those aged ≤60 years and with ≤5% marrow blasts, or those with hypocellular marrows, paroxysmal nocturnal hemoglobinuria [PNH] clone positivity, or STAT-3–mutant cytotoxic T-cell clones). IST includes equine ATG, with or without cyclosporin A, and with or without eltrombopag. A phase I/II trial examined the combination of IST with eltrombopag, a thrombopoietin (TPO) agonist also known as a TPO mimetic, in patients with aplastic anemia (not MDS).[7] Three cohorts were used that differed by the schedule for the start of treatment and the duration of treatment. The most common grade ≥3 adverse event attributed to eltrombopag was an abnormality in a liver test (18%), specifically transaminase elevation and/or hyperbilirubinemia. The complete hematologic response and overall response rate (ORR) for the combined cohorts at 6 months, when compared with a historical cohort of 102 patients who were treated with IST, were 39% (95% CI, 29%–49%) versus 10% and 87% (95% CI, 80%–94%) versus 66%, respectively. The rate of clonal evolution was not increased in patients who received eltrombopag compared with a historical cohort at the 2-year time point. A phase II trial with patients with aplastic anemia reported an ORR of 76% in those receiving the combination treatment compared with 71% in those treated with IST only.[8] The complete remission rate, median time to response, and survival rate at 2 years were

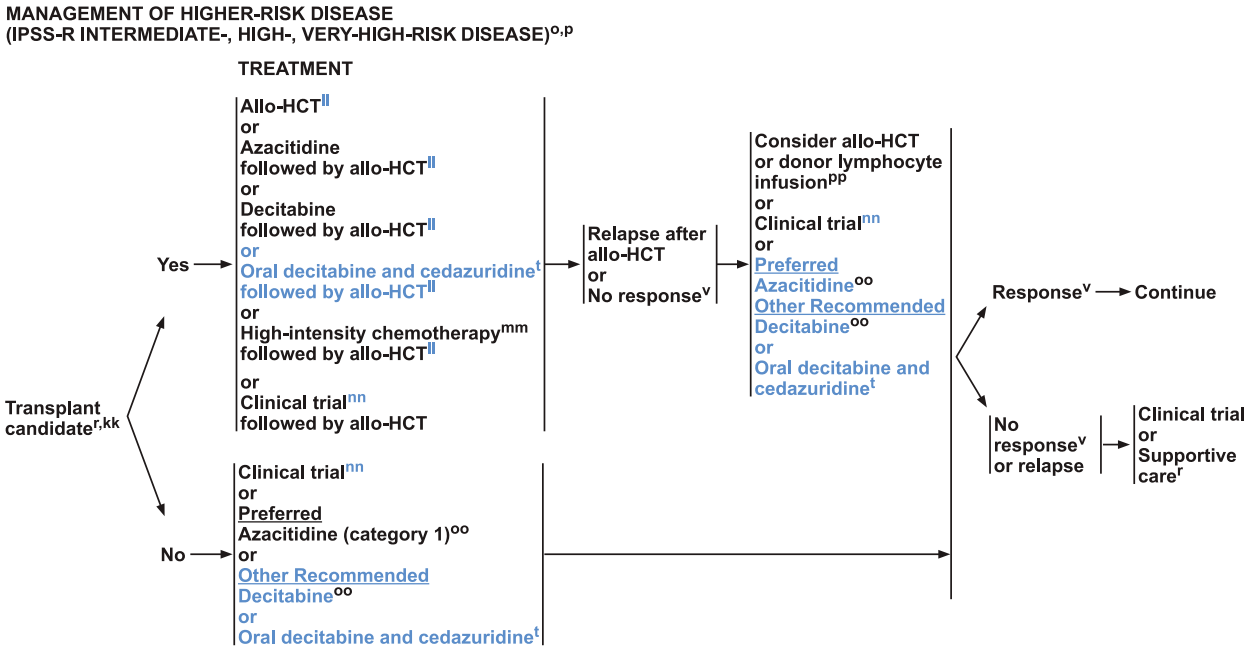
FOOTNOTES

[o] Presence of comorbidities should also be considered for evaluation of prognosis (See Comorbidity Indices in the Discussion).
[p] Given its more accurate risk stratification, the IPSS-R categorization is preferred although the other systems also have good value. IPSS-R Intermediate patients may be managed as lower risk if their score is ≤3.5 vs. higher risk if score is >3.5. Pfeilstöcker M, et al. Blood 2016;128:902-910.
[q] If the disease is initially managed as lower risk but fails to respond, move to higher risk management strategies.
[r] See Supportive Care (MDS-7 and MDS-8).
[t] Oral decitabine and cedazuridine (DEC-C) could be a substitution for intravenous decitabine in patients with IPSS Intermediate-1 and above. (Garcia-Manero G, et al. Blood 2020;136:674-683).
[v] Response should be evaluated based on IWG criteria: Cheson BD, et al. Blood 2006;108:419-425. Failure would be considered if no response within 3–6 mo.
[x] IPSS Intermediate-1, IPSS-R Intermediate, and WPSS Intermediate patients with severe cytopenias would also be considered candidates for HCT. Matched sibling, unrelated donor, or alternative (haploidentical or cord blood when appropriate) donor, including standard and reduced-intensity preparative approaches, may be considered.
[y] Refers predominantly to lower-risk IPSS-R and IPSS patients.
[z] Recommended initial dose is: 10 mg/day for 21 out of 28 days or 28 days monthly for 2–4 months to assess response (See Discussion). Alternative option to lenalidomide may include an initial trial of ESAs in patients with serum EPO ≤500 mU/mL. Use caution for patients with low platelet and neutrophil counts; consider modifying lenalidomide dose. Sekeres MA, et al. J Clin Oncol 2008;26:5943-5949. Patients with monosomy 7 are an exception and should be treated in the higher prognostic risk category (see MDS-6).
[aa] At some institutions, darbepoetin alfa has been administered using doses up to 500 mcg every other week.
[bb] Data have demonstrated the effectiveness of luspatercept for treating the anemia of ring sideroblastic (RS) lower-risk MDS patients. Fenaux P, et al. N Eng J Med 2020;382:140-151. For lower-risk MDS patients lacking RS treated with luspatercept, encouraging albeit limited data have emerged (36% HI-E in 44 patients) in abstract form [Platzbecker U, et al. Clin Lymphoma Myeloma Leuk 2020;20:S319-320 Abstract MDS-191]. However, FDA approval has not yet occurred for use of the drug for RS negative patients. We recommend such patients enter clinical trials for use of luspatercept.
[cc] Target hemoglobin range 10 to 12 g/dL; not to exceed 12 g/dL.
[dd] Lack of 1.5 gm/dL rise in hemoglobin or lack of a decrease in RBC transfusion requirement by 3 to 6 months of treatment.
[ee] Lack of 1.5 gm/dL rise in hemoglobin or lack of a decrease in RBC transfusion requirement by 6 to 8 weeks of treatment.
[ff] Lenalidomide 10 mg daily if ANC >0.5, platelets >50,000; Toma A, et al. Leukemia 2016;30:897-905.
[gg] Patients generally ≤60 y and with ≤5% marrow blasts, or those with hypocellular marrows, PNH clone positivity, or STAT-3 mutant cytotoxic T-cell clones. IST includes equine ATG ± cyclosporin A ± eltrombopag (category 2B for eltrombopag combinations).
[hh] Patients lack features listsed in footnote gg.
[ii] See dosing of hematopoietic cytokines. (MDS-4)
[jj] Emerging data are demonstrating effectiveness of ivosidenib and enasidenib for MDS patients with *IDH1/2* mutations (Medeiros BC, et al. Leukemia 2017;31:272-281).

similar in both groups. Concerns for potential proliferation of leukemic blasts in response to exogenous TPO have been raised in earlier in vitro studies, particularly for high-risk MDS.[9,10] Results from ongoing clinical trials with TPO mimetics will help elucidate the risks for leukemic transformations in patients with MDS. It should be noted that eltrombopag is not currently approved for use in patients with MDS. The panel voted to add eltrombopag as a treatment option in combination with ATG, with or without cyclosporin A, for patients with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities, with ring sideroblasts <15% (or ring sideroblasts <5% with an *SF3B1* mutation), serum erythropoietin >500 mU/mL, and good probability to respond to IST (see MDS-5 and MDS-5A, page 109 and above, respectively). Eltrombopag combinations are category 2B recommendations.

Following a panel vote, eltrombopag was added as a treatment option for patients with lower-risk MDS with certain cytopenias (see MDS-3, page 108). The panel updated a footnote to include that eltrombopag alone could be considered for severe thrombocytopenia. A phase II study enrolled patients with low-risk or IPSS int-1 risk MDS with severe thrombocytopenia who were randomized 2:1 to receive eltrombopag or placebo.[11] At the time of the interim analysis, in the intention-to-treat population, 47% of patients receiving eltrombopag demonstrated a platelet response, as opposed to 3% of patients in the placebo group ($P<.0001$; odds ratio, 27.1 [95% CI, 3.5–211.9; $P=.0017$]), and 46% of patients in the eltrombopag arm had grade 3/4 adverse events compared with 16% in the placebo group ($P=.0053$). Fewer bleeding events were reported in the eltrombopag arm compared with the placebo arm (14% vs 42%, respectively; $P=.0025$). Results from another phase II trial determined that eltrombopag monotherapy in patients with lower-risk MDS with cytopenia, including anemia, thrombocytopenia, or neutropenia, led to a 44% rate of hematologic response at 16 to 20 weeks.[12] A few patients acquired chromosomal abnormalities. A study by Fan et al[13] found that 50% of patients with moderate aplastic anemia or unilineage cytopenias (platelet count $<30 \times 10^9$/L or dependence on platelet transfusions or hemoglobin count <8.5 g/dL or dependence on RBC transfusions) treated with eltrombopag achieved a clinically meaningful response at 16 to 20 weeks. Of 34 patients, 2 acquired cytogenetic abnormalities.

The panel received an external request to consider the inclusion of luspatercept-aamt as a treatment option



See footnotes on page MDS-6A.

for patients with anemia and lower-risk MDS without ring sideroblasts. After a thorough discussion, the panel did not recommend luspatercept-aamt for such patients because the data are only available in abstract format[14] and the drug is not FDA-approved for this indication. The panel updated a footnote to highlight the emerging data on luspatercept-aamt for this group of patients and recommends such patients enroll in a clinical trial for the use of this agent (see MDS-5A, opposite page).

The panel members also discussed imetelstat, a telomerase inhibitor. Given that it is not FDA-approved, a decision was made to include information about imetelstat in the discussion section rather than in the algorithm. In a phase II trial comprising 57 patients with lower-risk MDS that had relapsed or was refractory to erythropoiesis-stimulating agents (ESAs) and who were RBC transfusion–dependent, treatment with imetelstat resulted in 37% and 23% rates of RBC transfusion independence (TI) at 8 and 24 weeks, respectively.[15] At the same time points, RBC-TI rates of 42% and 29%, respectively, were observed in a subgroup of 38 patients without del(5q) and who were not previously treated with a hypomethylating agent (HMA) or lenalidomide. The median duration for TI was 65 weeks for the overall group compared with 86 weeks in the subgroup. Hematologic improvement, in terms of erythroid response per the International Working Group 2006 response criteria, was achieved in 65% of patients in the overall group and 68% of patients in the subgroup. Overall, the most common grade ≥3 hematologic adverse events were neutropenia (60%), thrombocytopenia (54%), and anemia (19%). At 5%, the most common grade ≥3 nonhematologic adverse events were back pain, increased alanine aminotransferase, increased aspartate aminotransferase, and bronchitis.

Management of Higher-Risk MDS

The panel included the combination of oral decitabine and cedazuridine directly in the algorithm for patients with higher-risk MDS and noted that the combined oral formulation could be a substitution for intravenous decitabine in patients with IPSS int-1 and above (see MDS-6 and MDS-6A, above and page 112, respectively).[6] The panel also discussed recommendations for the management of higher-risk MDS and debated the merits of emerging therapies, such as the combination of venetoclax and HMAs, and noted that published phase III data

FOOTNOTES

[o] Presence of comorbidities should also be considered for evaluation of prognosis (See Comorbidity Indices in the Discussion).
[p] Given its more accurate risk stratification, the IPSS-R categorization is preferred although the other systems also have good value. IPSS-R Intermediate patients may be managed as lower risk if their score is ≤3.5 vs. higher risk if score is >3.5. Pfeilstöcker M, et al. Blood 2016;128:902-910.
[r] See Supportive Care (MDS-7 and MDS-8).
[t] Oral decitabine and cedazuridine (DEC-C) could be a substitution for intravenous decitabine in patients with IPSS Intermediate-1 and above. (Garcia-Manero G, et al. Blood 2020;136:674-683).
[v] Response should be evaluated based on IWG criteria: Cheson BD, et al. Blood 2006;108:419-425. Failure would be considered if no response within 3–6 mo.
[kk] Based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver, patients may be taken immediately to transplant or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant.
[ll] Allogeneic HCT from the most suitable donor (HLA-matched sibling or unrelated donor, HLA-haploidentical family member or cord blood). Early referral for transplant evaluation is recommended to allow moving to transplant efficiently. Pre-transplant debulking therapy to reduce marrow blasts to <5% with the goal of reducing post-transplant relapse (see footnote nn and Discussion) is recommended, although the optimum strategy (azacitidine, decitabine, induction-type chemotherapy) has not been determined. To reduce the disease burden pre-transplant is particularly important in patients who will receive a reduced-intensity conditioning regimen (Festuccia M, et al. Biol Blood Marrow Transplant 2016;22:1227-1233). At some centers, failure to achieve <5% blasts with cytoreduction should not preclude from proceeding to transplant, as these patients appeared to derive survival benefit from transplant (Nakamura R, et al. ASH Annual Meeting 2020:Abstract 75. Schroeder T, et al. Biol Blood Marrow Transplant 2019:25;1550-1559). Strategies for patients with specific mutations are under investigation. Patients with TP53 mutations, particularly biallelic, have a poor prognosis even with transplantation. These cases should be discussed with a transplant physician and patients should be enrolled in a clinical trial whenever possible.
[mm] High-intensity chemotherapy: Clinical trials with investigational therapy (preferred); or standard induction therapy if investigational protocol is unavailable or if it is used as a bridge to HCT.
[nn] Some emerging data have shown efficacy of novel agents, including venetoclax in combination with hypomethylating agents or targeted IDH1/2 inhibitors for cytoreduction for patients with high-risk MDS (DiNardo C, et al. N Engl J Med 2018;378:2386-2398) who have HMA-refractory disease. When used as cytoreduction for MDS in combination with HMA, venetoclax has been effectively given in monthly courses of 14 days (Garcia JS, et al. ASH Annual Meeting 2020:Abstract 656). Repeat of marrow evaluation after 1–2 cycles is important to clarify recovery of hematopoiesis and potential requirement for further therapy. Clinical trials are preferred. (See Discussion).
[oo] While the response rates are similar for both drugs, survival benefit from a phase III randomized trial is reported for azacitidine and not for decitabine. Azacitidine or decitabine therapy should be continued for at least 4–6 cycles to assess response to these agents. In patients who have clinical benefit, continue treatment with the hypomethylating agent as maintenance therapy.
[pp] Consider second transplant or donor lymphocyte infusion immuno-based therapy for appropriate patients who had a prolonged remission after first transplant.

for this combination are not available. There are also limited data for the use of targeted drugs such as IDH inhibitors for patients with MDS. As overexpression of the B-cell lymphoma 2 (BCL-2) protein has been linked to disease progression in MDS, studies are ongoing to investigate the efficacy and safety of venetoclax, a BCL-2 inhibitor, in patients with MDS either first-line or refractory or resistant to HMAs.[16–18] Preliminary results from a phase Ib study investigating the combination of venetoclax and azacitidine (AzaC) for 14 days in a 28-day cycle in up-front higher-risk MDS (IPSS int-2 or high) resulted in an ORR, median overall survival (OS), median progression-free survival, and median duration of response of 77%, not reached (95% CI, 16.2 months–not estimable), 17.5 months (14.5 months–not estimable), and 14.8 months (95% CI, 12.9 months–not estimable), respectively.[17] The most frequent grade ≥3 adverse events were neutropenia (51%), febrile neutropenia (46%), and thrombocytopenia (30%). In a study exploring venetoclax as a salvage agent alone or in combination, preliminary results showed an ORR of 7% with venetoclax alone compared with 50% with venetoclax/AzaC.[18] The panel updated a footnote to mention that emerging data have shown the efficacy of venetoclax in combination with HMAs or targeted IDH1/2 inhibitors for cytoreduction in patients with high-risk MDS[17,19] refractory to HMAs (see MDS-6A, above). When used as cytoreduction for MDS in combination with an HMA, venetoclax has been effectively given for 14 days in monthly courses.[17] Repeating the bone marrow evaluation after 1 to 2 cycles is important to clarify the recovery of hematopoiesis and potential requirement for further therapy.[17] Clinical trials are preferred (eg, ClinicalTrials.com identifier: NCT04401748).

Mutations in the *IDH1* or *IDH2* genes occur in approximately 4% to 12% of patients with MDS.[20–22] Ongoing clinical trials are investigating the efficacy of targeted IDH1/2 inhibitors in patients with MDS (NCT03503409, NCT03471260, and NCT03744390). A phase I trial evaluating the efficacy and safety of ivosidenib in patients with AML or MDS with an *IDH1* mutation[19] found that of 12 patients with MDS, 11 had an overall response, 5 of whom achieved complete remission. A phase I/II trial evaluating the efficacy and safety of enasidenib, an inhibitor of the mutant IDH2 protein, found a 53% ORR (95% CI, 28%–77%), a median OS of 16.9 months (95% CI, 1.5–32.3 months), and a median duration of response of 9.2 months

SUPPORTIVE CARE[r]

- Pre-transplant
  - Transplant and non-transplant patients should receive support.
  - Transfusion products should be irradiated with 25 Gy or per institution standard.
  - Patients with ≥5% marrow blasts who are candidates for reduced-intensity conditioning (RIC) are encouraged to receive "debulking" therapy with HMA or induction chemotherapy. Transplantation should be carried out as long as patients are responding; it should not be delayed until the response is lost.
- Clinical monitoring
  - Psychosocial support (See NCCN Guidelines for Survivorship)
  - Quality-of-life assessment
  - Transfusions[qq]:
    - ◊ RBC transfusions (CMV-safe) are recommended for symptomatic anemia, and platelet transfusions are recommended for thrombocytopenic bleeding. However, they should not be used routinely in patients with thrombocytopenia in the absence of bleeding unless platelet count <10,000/mcL. Irradiated products are suggested for transplant candidates.
  - Antibiotics are recommended for bacterial infections, but no routine prophylaxis is recommended except in patients with recurrent infections.
- Aminocaproic acid or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusions or profound thrombocytopenia.
- Iron chelation:
  - If >20 to 30 RBC transfusions have been received, consider daily chelation with deferoxamine subcutaneously or deferasirox orally to decrease iron overload, particularly for patients who have lower-risk MDS or who are potential transplant candidates (LOW/INT-1). For patients with serum ferritin levels >2500 ng/mL, aim to decrease ferritin levels to <1000 ng/mL.[rr] (See Discussion). Patients with low creatinine clearance (<40 mL/min) should not be treated with deferasirox or deferoxamine.

[r] See NCCN Guidelines for Supportive Care.
[qq] Avoid transfusions for arbitrary hemoglobin thresholds in the absence of symptoms of active coronary disease, heart failure, or stroke. In situations where transfusions are necessary, transfuse the minimum units necessary to relieve symptoms of anemia or to return the patient to a safe hemoglobin level. Hicks L, et al. Blood 2013;122:3879-3883.
[rr] Clinical trials in MDS are currently ongoing with oral chelating agents.

(95% CI, 1.0 month–not reached) in patients with MDS with an *IDH2* mutation.[23] Hyperbilirubinemia (35%), pneumonia (29%), and thrombocytopenia (24%) were the most frequent grade 3/4 treatment-emergent adverse occurrences. A phase II study in patients with higher-risk *IDH2*-mutated MDS/chronic myelomonocytic leukemia or low-blast AML determined an ORR, complete remission rate, and hematologic improvement rate of 84%, 24%, and 8%, respectively, in patients with no prior HMA treatment, compared with 43%, 24%, and 10%, respectively, in patients with disease that progressed or was refractory to HMA treatment.[24] Frequent treatment-related grade 3/4 adverse occurrences reported in the combination arm included neutropenia (64%), thrombocytopenia (28%), and anemia (8%), as opposed to 10%, 0%, and 5%, respectively, in the monotherapy arm.

HMAs are listed as treatment options for patients with higher-risk MDS who are not eligible for transplant or as a bridge to transplant. In 2021, the panel completed the stratification of systemic therapy recommendations for patients with higher-risk MDS (see MDS-6, page 111). AzaC is listed as "preferred," while decitabine and the combination of oral decitabine and cedazuridine are listed as "other recommended regimens," both for nontransplant candidates as well as for individuals with MDS that relapsed after allogeneic hematopoietic cell transplant or did not respond. Clinical trial is also an option for these patients. Although the response rates for AzaC and decitabine are similar, survival benefit from one phase III randomized trial has been reported for AzaC[25] and not for decitabine.

The panel also discussed the recent data regarding allogeneic hematopoietic cell transplant (HCT) versus continued HMA therapy for treating patients with higher-risk MDS, indicating a survival advantage for patients who underwent transplantation.[26] These data have since been published.[27] At 3 years, an intention-to-treat analysis revealed that the adjusted OS rate in patients aged 50 to 75 years was 47.9% (95% CI, 41.3%–54.1%) and 26.6% (95% CI, 18.4%–35.6%; *P*=.0001) for those in the donor arm (expected to undergo reduced-intensity conditioning HCT, n=260) and the no-donor arm (expected to receive HMA therapy or best supportive care, n=124), respectively. In addition, at the same time point, the leukemia-free survival rate was 35.8% (95% CI, 29.8%–41.8%) versus 20.6% (95% CI, 13.3%–29.1%; *P*=.003), respectively. Subgroup analyses showed no differences in outcomes by age ≤65 versus

SUPPORTIVE CARE[r]

- **Cytokines:**
  - **EPO: See Anemia Pathway (MDS-4)**
    - ◊ **EPO refers to the following agents: epoetin alfa and epoetin alfa-epbx.**
  - **G-CSF:**
    - ◊ **G-CSF refers to the following agents: filgrastim[ss] and tbo-filgrastim. Not recommended for routine infection prophylaxis.**
    - ◊ **Consider use in neutropenic patients with recurrent or resistant infections.**
    - ◊ **Combine with EPO for anemia when indicated. See Anemia Pathway (MDS-4).**
    - ◊ **Platelet count should be monitored.**
- **Clinically significant thrombocytopenia**
  - **In patients with lower-risk MDS who have severe or life-threatening thrombocytopenia, consider treatment with a thrombopoietin-receptor agonist.[tt]**
- **Post-transplant**
  - **Patients should receive antibiotic prophylaxis at least as long as they are on immunosuppressive therapy.**
  - **Detailed recommendations are provided in the Guidelines generated by the American Society of Transplantation and Cellular Therapy (ASTCT, formerly ASBMT). See NCCN Guidelines for Hematopoietic Cell Transplantation (HCT).**

[r] See NCCN Guidelines for Supportive Care.
[ss] An FDA-approved biosimilar is an appropriate substitute for filgrastim.
[tt] Giagounidis A, et al. Cancer 2014;120:1838-1846. Platzbecker U, et al. Lancet Haematol 2015;2:e417-e426. Oliva EN, et al. Lancet Haematol 2017;4:e127-e136.

MDS-8

>65 years. Another study examined retrospectively the outcomes of patients with high-risk MDS or secondary AML who underwent transplantation without prior cytoreductive therapy (n=67) compared with those who received cytoreductive therapy in the form of induction chemotherapy (n=64) or HMAs (n=34) prior to transplantation.[28] Patients had a blast count of ≥5% in the bone marrow. Reduced-intensity conditioning was applied before stem cell infusion in 68% of patients. Compared with the other groups, a higher percentage of patients in the HMA group (85%) were treated with a reduced-intensity conditioning regimen, which is likely due to the difference in age. Multivariate analyses revealed that the type of pretransplant treatment did not impact OS, relapse-free survival (RFS), and nonrelapse mortality. However, cytogenetics, reduced-intensity conditioning, and use of an unrelated donor were found to be predictors of negative outcomes. At 5 years, there was no difference in OS (61%, 50%, and 45%, respectively; *P*=.116) and RFS (38%, 41%, and 38%, respectively; *P*=.926) between the 3 groups. OS (*P*=.971) and RFS (*P*=.883) were similar in patients with blasts <10% or ≥10% in the bone marrow who underwent transplantation without prior cytoreductive therapy.

Based on the positive results of the donor versus no-donor analysis,[26,27] a footnote was amended to clarify that early referral to transplant is recommended to allow moving to transplant efficiently (see MDS-6A, page 112). Pretransplant debulking therapy to reduce marrow blasts to <5% blasts with the goal of reducing posttransplant relapse is recommended, although the optimum strategy has not been determined. Reducing the disease burden pretransplant is particularly important in patients who will receive a reduced-intensity conditioning regimen.[29] At some centers, failure to achieve <5% blasts with cytoreduction did not preclude from proceeding to transplant, as these patients appeared to derive survival benefit from transplant.[27,28]

An argument in favor of pretransplant cytoreduction was provided by Festuccia et al,[29] who showed that the presence of minimal identifiable disease (MID) prior to transplantation in patients with MDS or AML arising from MDS impacted prognosis following transplantation. Among patients who were MID-positive by cytogenetics, irrespective of positivity by flow cytometry, the overall mortality risk was higher in those who underwent low-intensity conditioning compared with those who underwent high-intensity conditioning. However, in patients with an

GENETIC FAMILIAL HIGH-RISK ASSESSMENT: HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES

4. Post-test counseling done when the test results are disclosed
- **Discuss results and associated medical risks.**
- **Interpret results in context of patient's presentation.**
- **Discuss recommended medical management.**
- **Discuss and offer assistance with information and testing at-risk family members.**
- **Discuss available resources such as high-risk clinics, disease-specific support groups, and research studies.**
- **For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic diagnosis.**
- **Consider carrier status implications of certain autosomal recessive disorders.**

5. Limitations of the proposed approach
- **The current criteria are focused mainly on known genetic predisposition syndromes to MDS or AML. The proposed age threshold of 50 years at the time of diagnosis is arbitrary and conditions known to be diagnosed at older ages (*DDX41*) with predisposition to MDS or AML due to germline may be missed. Additionally, there are certainly genetic aberrations predisposing to the development of myeloid neoplasms that have not yet been identified and as such, some patients may not fit the aforementioned criteria. Any clinical suspicion of a hereditary condition not included in these guidelines may still warrant a referral to an institution with expertise in the field.**

6. Surveillance
- **Individuals who fulfill the clinical diagnostic criteria for a myeloid neoplasm with a germline predisposition should undergo surveillance, even if the pathogenic genetic variant is undetermined.**
- **Individuals with a deleterious or likely deleterious genetic variant associated with a germline predisposition should undergo surveillance, regardless of clinical presentation.**

[6] Wong JC, Bryant V, Lamprecht T, et al. Germline *SAMD9* and *SAMD9L* mutations are associated with extensive genetic evolution and diverse hematologic outcomes. JCI Insight 2018;3:e121086.
[7] Tesi B, Davidsson J, Voss M, et al. Gain-of-function *SAMD9*L mutations cause a syndrome of cytopenia, immunodeficiency, MDS, and neurological symptoms. Blood 2017;129:2266-2279.
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Continued

MID-negative status, as determined by both cytogenetics and flow cytometry, the risk of mortality with low- and high-intensity conditioning regimens was similar. It is important to note that this study did not specifically examine outcomes in patients who proceeded to transplant without cytoreductive therapy. Among patients with an MID-positive status, as assessed by both cytogenetics and flow cytometry, the risk of relapse was higher in those who underwent low-intensity conditioning, as opposed to those who underwent high-intensity conditioning. As the MID classification can help identify patient subgroups that may have better outcomes with high- or low-intensity conditioning, the authors propose considering the presence of MID to help determine the intensity of the conditioning regimen for patients being considered for transplant.

Supportive Care

Supportive care is an important aspect of MDS management, which entails observation, clinical monitoring, psychosocial support, and quality-of-life (QoL) assessment. In the 2022 update, the panel included some new recommendations for the pretransplant and posttransplant settings (see MDS-7 and MDS-8, page 113 and opposite page, respectively). Prior to transplant, transplant patients should receive support. Transfusion products should be irradiated with 25 Gy or per institution standard. Patients with ≥5% marrow blasts who are candidates for reduced-intensity conditioning are encouraged to receive "debulking" therapy with an HMA or induction chemotherapy. Transplantation should be carried out as long as patients are experiencing response and should not be delayed until the response is lost. Posttransplantation, patients should receive antibiotic prophylaxis at least as long as they are on immunosuppressive therapy. Detailed recommendations are provided in the guidelines generated by the American Society of Transplantation and Cellular Therapy[30] and the NCCN Guidelines for Hematopoietic Cell Transplantation (available at NCCN.org).

Genetic Familial High-Risk Assessment: Hereditary Myeloid Malignancy Predisposition Syndromes

Molecular and genetic screening for hereditary hematologic malignancy predisposition is recommended in a subset of patients, particularly those aged <50 years. Diseases, syndromes, and mutations that may potentially be

associated include GATA2 deficiency syndrome, Shwachman-Diamond syndrome, short telomere syndromes, *DDX41* mutations (usually present at older ages), and others (see "Genetic/Familial High-Risk Assessment: Hereditary Myeloid Malignancy Predisposition Syndromes" and "Gene Mutations Associated with Hereditary Myeloid Malignancies" in the full algorithm at NCCN.org). This year, a subcommittee of the NCCN MDS Panel worked on updating recommendations for genetic familial high-risk assessment of hereditary myeloid malignancy predisposition syndromes. The subcommittee members discussed the new proposed content and panel members reviewed the content during the panel review process. The guidelines include information about pretest counseling prior to ordering testing, appropriate DNA source for germline genetic testing, consideration of the appropriate genetic testing methodologies and other diagnostic testing, and postcounseling performed when the test results are disclosed. In this update, limitations of the proposed approach were added to the recommendations, as well as recommendations about which patients should undergo surveillance, namely individuals who fulfill the clinical diagnostic criteria for a myeloid neoplasm with a germline predisposition (even if the pathogenic variant is undetermined), as well as individuals with a deleterious or likely deleterious genetic variant associated with a germline predisposition, regardless of clinical presentation (see MDS-D 4 of 5, page 115). In the evaluation for suspected hereditary myeloid malignancy predisposition syndromes, the panel included individuals with aberrations of chromosome 7 and age <50 years among individuals for whom testing is recommended, and also updated allogeneic sibling donor to allogeneic related donor in this setting. The panel also included information about some newly added germline gene mutations that are associated with hereditary myeloid malignancies, more specifically XPC^{delTG}, *ERCC6L2*, and *LIG-4*.[31–36]

Conclusions

The NCCN Guidelines for MDS are based on extensive evaluation of the reviewed risk-based data and indicate current approaches for managing patients with MDS. These NCCN Guidelines Insights highlight some of the updated recommendations, preference stratification, and emerging data on novel agents. Treatment options vary based on the risk category and clinical characteristics. Ongoing clinical trials are underway to investigate new therapeutic avenues, and the results of these trials may help inform the panel's recommendations.

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