International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

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The classification of myeloid neoplasms and acute leukemias was last updated in 2016 within a collaboration between the World Health Organization (WHO), the Society for Hematopathology, and the European Association for Haematopathology. This collaboration was primarily based on input from a clinical advisory committees (CACs) composed of pathologists, hematologists, oncologists, geneticists, and bioin- formaticians from around the world. The recent advances in our understanding of the biology of hematologic malignancies, the experience with the use of the 2016 WHO classification in clinical practice, and the results of clinical trials have indicated the need for further revising and updating the classification. As a continuation of this CAC-based process, the authors, a group with expertise in the clinical, pathologic, and genetic aspects of these disorders, developed the International Consensus Classification (ICC) of myeloid neoplasms and acute leukemias. Using a multiparameter approach, the main objective of the consensus process was the definition of real disease entities, including the introduction of new entities and refined criteria for existing diagnostic categories, based on accumulated data. The ICC is aimed at facilitating diagnosis and prognostication of these neoplasms, improving treatment of affected patients, and allowing the design of innovative clinical trials.

Introduction

The third, fourth and revised fourth editions of the World Health Organization (WHO) Classification of the Tumors of Hematopoi- etic and Lymphoid Tissues[1-3] were collaborations between the WHO, the Society for Hematopathology (SH), and the European Association for Haematopathology (EAHP) based on input from clinical advisory committees (CACs) composed of numerous pathologists, hematologists, oncologists, and geneticists. The outcome of those CACs were published in peer-reviewed jour- nals and ultimately resulted in the “blue book” monographs.[4-8] As described in more detail elsewhere[9] and the commentary in this issue, the fifth edition blue book series as planned by the International Agency for Research on Cancer (IARC) lacked over- sight of SH and EAHP and did not follow a CAC process. Ulti- mately, a CAC endorsed by SH and EAHP, separate from the WHO, was held to update the prior classification. Because it was a revision of the prior fourth edition, the revised fourth edition WHO classification, published in 2016, was tasked to not be a major overhaul of disease categories but simply as an update based on new knowledge. Major advances in the understanding of myeloid neoplasms and acute leukemia have occurred since the original fourth edition publication in 2008, and a more signif- icant change to disease classification is now warranted. This new classification represents a major revision of the prior classifica- tions and includes many authors of the prior WHO editions but is no longer affiliated with the WHO. This report summarizes the new International Consensus Classification (ICC) with a focus on myeloid neoplasms and acute leukemia (Table 1). A separately published report will summarize the ICC of lymphoid neoplasms which together constitute the International Consensus Classifica- tion of Myeloid and Lymphoid Neoplasms.

Myeloproliferative neoplasms

The major categories of myeloproliferative neoplasms (MPN)[3] remain unchanged in the ICC; however, continuous integration of new molecular data and improved understanding of morphol- ogy have sharpened the proposed diagnostic criteria.[10,11]

In chronic myeloid leukemia (CML), progression to advanced phases[12-14] (Table 2) is a consequence of continued BCR::ABL1 activity, induced proliferation of leukemic cells, and further genetic instability and DNA damage.[15] This invariably leads to clonal evolution and acquisitions of mutations both inside and outside the BCR::ABL1 kinase domain and additional chromo- somal abnormalities (ACAs). Therefore, the presence of major route ACAs at diagnosis or the acquisition of major route ACAs on treatment are considered as the hallmark of CML in acceler- ated phase (CML-AP),[14,16] although most ACAs were defined prior to the use of tyrosine kinase inhibitor therapy. A bone mar- row (BM) trephine biopsy is indicated for patients who meet any of the criteria for CML-AP or blast phase (CML-BP) and for patients who have a clinical history suggestive of disease pro- gression (eg, progressive splenomegaly). Importantly, an increase in BM reticulin fibers at the time of diagnosis is corre- lated with a decreased major molecular response rate in the first year of tyrosine kinase inhibitor therapy.[17] The ICC has main- tained a blast percentage threshold of 10% to 19% and at least 20% in the blood or BM to establish the diagnosis of AP and BP, respectively. Increasing numbers of lymphoblasts (.5%) in peripheral blood (PB) or BM may indicate impending lymphoid BP and thus should prompt further laboratory and genetic stud- ies.[18] Of note, other classification and risk stratification systems that include the International Blood and Marrow Transplant Reg- istry,[19] M. D. Anderson Cancer Center,[20] and the European Leu- kemiaNet[21] have defined a higher blast threshold of more than 30% for BP and are frequently used as eligibility criteria in clini- cal trials.[12,21] The classical BCR::ABL1-negative MPN subtypes include polycy- themia vera (PV) (Table 3), essential thrombocythemia (ET) (Table 4), and primary myelofibrosis (PMF) (Table 5). The princi- pal objective in the classification of these cases is to reduce diagnostic uncertainty especially in initial/early disease stages presenting with elevated platelet counts and to optimize clinical management of patients.[10] The integration of molecular findings with BM morphology and blood counts remains the cornerstone of diagnosis. Importantly, morphologic diagnosis should not only focus on megakaryocytic atypia but has to consider charac- teristic patterns of other features like age-related cellularity, changes in erythropoiesis, and neutrophil granulopoiesis in con- text with the grade of BM fibrosis.[22] Following the 2016 revision of the WHO classification, an increasing number of investigators were able to validate the diagnostic accuracy of this approach and consequently strongly support the definition of an early/ pre-fibrotic stage of PMF (pre-PMF).[23-26] In this context, dense clustering of megakaryocytes (3 or more megakaryocytes lying adjacent without other BM cells in between), which is generally accepted as the morphologic hallmark of PMF,[22,27] does not exclude the diagnosis of ET, because infrequently small megakaryocytic clusters may be present even in this subtype. Compared with pre-PMF, patients with ET usually present with normal white blood cell counts, no anemia, normal lactate dehydrogenase (LDH) values, less frequently splenomegaly, and lower numbers of CD34-positive progenitor cells in PB and BM.[23,24,26] Distinction is important because ET has a lower risk for major hemorrhagic events, a significantly lower risk of mye- lofibrotic progression (ie, post-ET myelofibrosis) ranging between 0.8% and 4.5% at 10 years, and a very low risk of transformation to BP with more than 20% of PB/BM blasts with a reported 10-year cumulative incidence between 0.7% and 1.9%.[28,29] Accurate identification of MPN-associated driver mutations, JAK2 V617F, JAK2 exon 12, MPL W515L/K, and calreticulin (CALR) by highly sensitive single target (quantitative reverse transcriptase-polymerase chain reaction [RT-qPCR], digital droplet PCR [ddPCR]) or multitarget panel/next generation sequenc- ing (NGS) assays with a minimal sensitivity of variant allele frequency (VAF) 1%, is important to support a diagnosis of PV, ET, or PMF and to separate wild-type or triple-negative cases.[30,31] In triple-negative cases, the search for noncanonical JAK2 and MPL mutations (the latter for suspected ET and PMF) is encouraged, whereas a JAK2 V617F VAF of ,1% should prompt the search for coexisting canonical CALR (and MPL) mutations. In PV, high VAF for JAK2 V617F is associated with older age, higher hemoglobin level, leukocytosis, and lower platelet count.[32] JAK2 exon 12 mutated cases are prognosti- cally similar to JAK2 V617F mutated cases, although they may occur at a younger age. Because a proportion of these cases may be characterized by isolated erythrocytosis associated with erythroid preponderance in the BM, the diagnostic criterion of panmyelosis may not be applicable to this patient subset. Chronic neutrophilic leukemia (CNL) is a rare BCR::ABL1 negative MPN (Table 6) characterized by persistent neutrophilia and often splenomegaly. Most patients with CNL have a poor prognosis, with a mean overall survival of 1.8 years.[33] The presence of driver mutations in the colony-stimulating factor 3 receptor (CSF3R) is the diagnostic genetic signature of CNL.[34-36] However, additional mutations can be seen in most cases. These include SETBP1, ASXL1, and SRSF2, as well as signaling mutations. The absence of a CSF3R mutation does not exclude the possibility of CNL.[35,37] At initial diagnosis of CNL, a predominance of granulocytes ($80%) at the segmented or band stage in the PB is characteristic, whereas significant monocytosis, basophilia, eosino- philia, or the presence of dysgranulopoiesis should prompt a criti- cal review of the diagnosis. In contrast to previously established criteria, the ICC suggests lowering the key diagnostic threshold for leukocytosis from $25 to $13 3 10^9/L in cases with CSF3R T618I or other activating CSF3R mutation. Because of expanded neutrophilic granulopoiesis in the BM, CNL is uniformly hypercellular with a myeloid to erythroid ratio that may exceed 20:1. In most cases, there are fewer than 5% myeloblasts and an absence of Auer rods, and there should be no dysplastic features in the granulocytic series. Increased numbers of circulating or BM blasts (10%-19%) along with progressive splenomegaly and wors- ening of thrombocytopenia indicate transformation to an AP, whereas $20% defines BP.[38]

Chronic eosinophilic leukemia, not otherwise specified (CEL, NOS) is an MPN characterized by persistent eosinophilia not meeting the criteria for other genetically defined enti- ties (Table 7). Mutations by NGS have helped to establish clonality in a significant subset of cases with eosinophilic disorders.[39-42] However, like other myeloid neoplasms, the application of NGS data in eosinophilic disorders can be challenging because of the prevalence of clonal hematopoi- esis of indeterminate potential (CHIP) and technical limitations in using NGS data to define clonality. The BM of CEL, NOS typically shows hypercellularity with dysplastic mega- karyocytes, with or without dysplastic features in other line- ages, and often significant fibrosis associated with an eosinophilic infiltrate.[43,44] Abnormal BM histopathology is now incorporated into the diagnostic criteria for CEL, NOS, allowing for a more definitive confirmation of the neoplastic nature of CEL, NOS and providing a better separation from the related entities idiopathic hypereosinophilic syndromes (iHES) and HE of unknown significance (HEus).[45] iHES is characterized by (1) persistent PB hypereosinophilia; (2) organ damage related to infiltration by eosinophils; and (3) no known reactive, familial, or neoplastic etiology, as well as exclusion of lymphocyte-variant HES.[46] HEus presents with persistent HE, but has no associated organ damage.

Except for increased eosinophils, the BM of iHES and HEus is morphologically unremarkable.[43,47] The refined criteria for CEL, NOS and iHES are shown in Tables 7 and 8. MPN, unclassifiable (MPN-U) is an appropriate diagnosis for cases presenting with clinical, morphologic, and molecular fea- tures (Table 9) that prevent a clear diagnosis of a specific MPN subtype.[10,48-50] In addition, this category is appropriate for patients presenting in very early-phase disease in which the required diagnostic features are not yet fully developed and rel- evant diagnostic thresholds not met. These cases need to be closely monitored to identify their specific MPN subtype, which tends to become manifest at follow-up. The category is also used to capture patients presenting with splanchnic or portal vein thrombosis that fail to meet specific criteria for a given MPN subtype. In cases with significant dysgranulopoiesis, dyser- ythropoiesis, or absolute monocytosis at the time of diagnosis, integration of molecular data and careful assessment of BM fea- tures is key to distinguish from myelodysplastic syndrome (MDS) or MDS/MPN and from advanced-stage MPN in disease pro- gression.[51] Of note, MPN-U may include cases with molecular evidence of MPN, in which a coexisting neoplastic or inflamma- tory disorder may obscure some of the characteristic morpho- logical diagnostic features.[10]

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

The category name is changed from the prior myeloid/lymphoid neoplasm with eosinophilia (M/LN-eo) and gene rearrangement to M/LN-eo with tyrosine kinase (TK) gene fusions (Table 10) to specify the molecular genetic changes underlying these hemato- poietic neoplasms. M/LN-eo frequently manifests as a chronic myeloid neoplasm with eosinophilia, clinically and histopatho- logically resembling CEL, NOS, other MPN, myelodysplastic/ myeloproliferative neoplasm (MDS/MPN), MDS, or systemic mastocytosis (SM), or presents as T- or B-acute lymphoblastic leukemia/lymphoma (ALL), acute myeloid leukemia (AML), BP of MPN, or mixed phenotype acute leukemia (MPAL).[52,53] Extrame- dullary presentation or involvement is common. For cases pre- senting as ALL with TK gene fusions, M/LN-eo differs from BCR::ABL1–like B-acute lymphoblastic leukemia (B-ALL) and de novo T-acute lymphoblastic leukemia (T-ALL) in its involvement not only of the lymphoblasts but also the background myeloid cells. Supported by a number of studies[53-55] after the initial pro- posal as a provisional entity,[8] M/LN-eo with t(8;9)(p22;p24.1)/ PCM1::JAK2 is now accepted as a formal member of this cate- gory. Other JAK2-rearranged neoplasms,[53-56] such as t(9;12)(p24.1;p13.2)/ETV6::JAK2 and t(9;22)(p24.1;q11.2)/ BCR::JAK2, show less distinctive histopathologic features such as characteristic erythroid microtumors[57] of PCM1::JAK2 but demonstrate similar clinical and genetic features and are consid- ered genetic variants of t(8;9)(p22;p24.1)/PCM1::JAK2. New additions to the category include M/LN-eo with t(9;12)(q34.1;p13.2)/ETV6::ABL1 and M/LN-eo with FLT3-rear- rangement. The most common FLT3 rearrangement[58-61] is t(12;13)(p13.2;q12.2)/ETV6::FLT3, whereas various other partner genes have been reported (Table 10). FLT3-rearranged M/LN- eo frequently presents with T-ALL or myeloid sarcoma associ- ated with MPN-like features in BM with or without eosinophilia. Irrespective of partner genes, FLT3-rearranged M/LN-eo appears to be sensitive to FLT3 inhibitors.[59-61] M/LN-eo with t(9;12)(q34.1;p13.2)/ETV6::ABL1[55,62,63] share a number of clinical and laboratory features with CML with frequent eosinophilia, mostly presenting in chronic phase, and some in myeloblastic or lymphoblastic phase. Tyrosine kinase inhibitors (TKIs), especially second-generation TKIs,[55] have shown therapeutic benefit for patients with ETV6::ABL1. ABL1 with other fusion partner genes[64] (other than the well-known BCR::ABL1 in CML), mostly presents as BCR::ABL1–like B-ALL[65] or de novo T-ALL,[66] very rarely manifesting as a myeloid neoplasm. However, with increased use of RNA sequencing technology in clinical samples, additional cryptic lesions may be identified in M/LN-eo with ABL1 rearrangement.

Mastocytosis

Mastocytosis is a neoplastic disease characterized by infiltration of clonal mast cells in different tissues, including BM, skin, the gastrointestinal tract, the liver, and/or the spleen.[67] There are 2 main types of mastocytosis: cutaneous mastocytosis, which mainly affects children and where the disease is almost always confined to the skin, and SM characterized by extracutaneous involvement with or without evidence of skin involvement. The 5 SM subtypes (also termed variants) are indolent SM (ISM), smoldering SM (SSM), aggressive SM (ASM), mast cell leukemia, and SM with an associated hematologic neoplasm (SM-AHN). The latter subtype name is changed in the ICC to SM with an associated myeloid neoplasm (SM-AMN; supple- mental Table 1 available on the Blood Web site). A clinico-pathologic variant of ISM termed BM mastocytosis (BMM), characterized by a limited degree of BM infiltration, no skin lesions, normal or slightly elevated serum tryptase levels, older age, male predominance, and a strong association with severe allergic reactions to Hymenoptera sting, has also been described.[68,69]

The ICC has introduced refinements to the criteria for diagnos- ing SM (Table 11). These criteria are largely based on morphol- ogy. Because the pathognomonic multifocal dense mast cell aggregates may not be readily recognized in routinely stained sections, demonstration of tryptase and KIT (CD117) immunore- activity has been added to ensure proper identification of mast cells.[70] CD30, which is found aberrantly expressed in a significant proportion of SM cases, has been added as an additional immunophenotypic finding to the second minor criteria.[71] An important modification addressing the presence of eosinophilia associated with a mast cell proliferation[53,72-77] is that the identifi- cation of 1 of the tyrosine kinase gene fusions associated with M/LN-Eo excludes a diagnosis of SM. The "burden of disease" criteria (ie, "B" findings), which have been used to differentiate smoldering SM from indolent SM, have been simplified particularly in relation to criterion 2 (supplemental Table 2). "C" findings are unchanged from the prior classification. In mastocytosis, the cytology of the mast cells is variable but atypical cytologic features (eg, marked spindling and hypogra- nularity) are almost always present. More pronounced degrees of cytologic atypia characterizes the aggressive SM variants. Mast cell leukemia, in particular, is defined as a proliferation of atypical immature mast cells including promastocytes, metachro- matic blast-like forms, and multinucleated or highly pleomorphic mast cells.[78] These atypical immature mast cells must account for $20% of the BM cellularity (supplemental Table 3). A provi- sion is made for diagnosing mast cell leukemia in the presence of a dry tap or an otherwise suboptimal BM aspirate. It is well recognized that mast cell leukemia may have circulating mast cells in a significant proportion of cases. It is recommended to document their presence in view of their prognostic relevance; however, the amount of circulating mast cells does not justify a separate subcategory of leukemic vs aleukemic mast cell leukemia. Rare cases of SM characterized by a proliferation of mature, round shaped, well-granulated mast cells can also be observed. These cases which typically lack KIT D816V mutation, are often characterized by a CD25-negative, CD2-negative, CD30-positive mast cell immunophenotype and variable serum tryptase. They may display a higher rate of response to conventional tyrosine kinase ihibitors. The SM subtype of SM-AHN is now modified to SM with an associated myeloid neoplasm (AMN), which allows a better framing of this disease entity (Table 12). Published work has demonstrated that the "hybrid" uniqueness of SM-AHN is lim- ited to the presence of an associated myeloid neoplasm, with which it often also shares a KIT mutation and/or other clonal genetic abnormalities. In contrast, presence of KIT mutation is not observed in lymphoid neoplasms that can occur concomi- tantly with SM.[79,80] SM-AMN is an aggressive neoplasm, and its diagnosis should clearly indicate the precise nature of both com- ponents, which need to be separately classified and appropri- ately managed.

MDS/MPN

The MDS/MPN category comprises a heterogeneous group of diseases characterized by the co-occurrence of clinical and path- ologic features of both myelodysplastic and myeloproliferative neoplasms.[81] The 2016 classification included chronic myelomo- nocytic leukemia (CMML), atypical CML, BCR::ABL1 negative (aCML), juvenile myelomonocytic leukemia (JMML), MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T), and MDS/MPN unclassifiable (MDS/MPN-U). The ICC now expands on these categories and moves JMML to be grouped with pedi- atric and/or germline mutation associated disorders. The major changes in the classification of MDS/MPN and their rationale are presented herewith. They are summarized in Tables 13 to 19. MDS/MPN are hybrid neoplastic myeloid diseases in which a myeloproliferative component coexists together with ineffective hematopoiesis leading to cytopenia. The lack of cytopenia as 1 of the explicit diagnostic requirements has muddled the distinc- tion of MDS/MPN from MPN and from reactive noncytopenic conditions characterized by monocytosis and/or leukocytosis. Reliance on evidence of dysplasia, which can often be subtle (eg, in CMML cases), and/or subjective as a “surrogate marker” for ineffective hematopoiesis, seems unwarranted. Therefore now “cytopenia” in combination with “cytosis” becomes one of the stated key characteristics of the MDS/MPN diseases. The definition of cytopenia follows what is being used in MDS: ane- mia, hemoglobin , 13 g/dL (males), , 12 g/dL (females); neu- tropenia, absolute neutrophil count , 1.8 3 10^9/L; thrombocytopenia, platelets , 150 3 10^9/L.[82] An exception to the necessity of cytopenia is represented by patients with early- stage CMML who in a small proportion of cases may show only borderline or no cytopenia. Those cases would require marrow morphology, flow cytometric, and molecular data to support a diagnosis of CMML.[83] The proliferative component in CMML is manifested as monocytosis often in association with splenomeg- aly and/or leukocytosis. The latter is characteristically seen in the myeloproliferative subtype of CMML (CMML-MP). Leukocytosis is also part of the definition of aCML and thrombocytosis of MDS/MPN-RS-T, whereas MDS/MPN, NOS requires leukocytosis and/or thrombocytosis.

CMML (Table 13)

The 2016 revision of the WHO classification introduced a 3-tier classification of CMML based blast percentage by adding CMML-0 for cases with ,2% blasts in PB and ,5% blasts in BM.[84] However, recent studies have shown that the prognostic impact of CMML-0 is absent or at best limited.[85,86] In addition, there is poor reproducibility in the setting of low blast counts, particularly in the case of CMML in which blasts include promon- ocytes whose distinction from abnormal monocytes can at times be problematic.[87] Thus, an additional change includes reverting to the fourth edition version 2-tiered system of CMML-1 (,5% blasts in PB, ,10% in BM) and CMML-2 (5%-19% blasts PB, 10%-19% in BM, or Auer rods); CMML-0 is eliminated. Mutations in splicing genes and epigenetic modifiers (eg, SRSF2, TET2, and/or ASXL1) are frequent in CMML and occur in up to 80% of cases. Other mutated genes that also occur com- monly at lower frequency include SETBP1, NRAS/KRAS, RUNX1, CBL, and EZH2. Overall, .90% of patients with CMML would be expected to show at least 1 of these mutations with modern sequencing capabilities.[83,88-90] Therefore, presence of mutations as a means to demonstrate clonality was felt to be critical for confirming a diagnosis of CMML. Having established the need for clonal- ity as 1 of the necessary diagnostic criteria, the presence of dysplasia as a surrogate marker of clonality becomes necessary only for rare patients who do not demonstrate a CMML-associated mutation. In addition to establishing clonality, mutations in CMML have prognostic implications (eg, ASXL1 mutations).[89,91-93] Of note, NPM1 mutation is seen in a rare subset of CMML (3%-5%), where it appears to herald a particularly aggressive clinical course with rapid progression to acute leukemia.[94] The development of an NPM1 mutation in CMML should be noted, but such a finding does not define de novo AML in the setting of known CMML. The integration of molecular genetics has further demonstrated that the so-called “oligomonocytic” CMML (cases with $10% circulating monocytes but an absolute monocyte count of 0.5 to ,1.0 3 10^{9}/L) and traditional CMML (absolute monocytes $ 1.0 3 10^{9}/L) share a similar genetic profile and should be consid- ered 1 disease.[95,96] Consequently, in the presence of clonality the modified criteria for diagnosing CMML now require a lower level of absolute monocytosis, $0.5 3 10^{9}/L; however, mono- cytes must still comprise $10% of the white blood cell count (WBC). Recent work has further confirmed the importance of identifying the myeloproliferative subtype of CMML (CMML-MP). In com- parison with the myelodysplastic subtype, CMML-MP (cases with WBC of .13 3 10^{9}/L) is frequently associated with mutations affecting the RAS pathway (eg, NRAS, KRAS, CBL) and JAK2 V617F and SETBP1 mutations. The adverse prognosis of CMML- MP is captured by various CMML-specific prognostic scoring systems,[89,91-93] and its diagnostic recognition may help in devel- oping innovative therapeutic strategies specifically tailored to those patients.

Clonal monocytosis of undetermined significance (Table 14)

Targeted sequencing in patients without signs of an overt mye- loid neoplasm has revealed clonal hematopoietic states, which are also included elsewhere in this consensus report. In reported cases with persistent mild monocytosis, evidence of clonal hema- topoiesis (CH) but indeterminate BM features not fulfilling criteria for CMML introduces specific forms of CH that predispose for an increased risk of MDS/MPNs. The types of myeloid mutations, number of mutations, and variant allele frequency largely but do not entirely overlap with overt CMML and are associated with higher risk of developing an overt myeloid malignancy.[83,97] Notably, among patients with clonal cytopenia of undetermined significance (CCUS), a monocytosis $10% and $0.5 3 10^{9}/L of the WBC almost invariably segregated precursor conditions with potential to progress to MDS/MPN.[97] Thus, the ICC recognizes the CMML precursor condition of clonal monocytosis of unde- termined significance (CMUS), based on persistent monocytosis (monocytes $ 10% and $ 0.5 3 10^{9}/L of the WBC), in the pres- ence of myeloid neoplasm-associated mutation(s) without BM morphologic findings of CMML. If cytopenia is present, the nomenclature of clonal cytopenia and monocytosis of undeter- mined significance (CCMUS) is suggested.

aCML (Table 15)

Because the absence of BCR::ABL1 is a requirement for diagnosing all subtypes of MDS/MPN, the notation “BCR::ABL1 negative” is now dropped from the name aCML. It is also now explicitly acknowledged that aCML is not characterized by eosinophilia: eosinophils should account for ,10% of the WBC,[98] and hypereosinophilia is clearly incompatible with this diagnosis. Having excluded the presence of significant eosinophilia, aCML can now be more easily separated from chronic eosinophilic leukemia, NOS, which can have variable morphologic dysplasia.[43] Although the presence of $10% circulating neutrophilic precursors and the usually severe granulocytic dysplasia support the neoplastic nature of the granulocytic proliferation in most cases, genetic analysis, which is always recommended, may be necessary to exclude M/LN-Eo (eosinophilia maybe absent in some cases) or other myeloid neoplasms, particu- larly from advanced-stage MPN, where myelodysplasia-like features can be encountered. In the latter setting, the absence of MPN-associated driver mutations (JAK2, CALR, MPL) is of diagnostic value in supporting a diagnosis of aCML.[99] A history of MPN and/or the presence of MPN- associated mutations (in JAK2, CALR, or MPL) tend to exclude the diagnosis of aCML; conversely, the diagnosis is supported by the presence of SETBP1 mutations often in association with comutated ASXL1. CSF3R mutation is uncommon, and, if detected, should prompt a careful mor- phologic review to exclude an alternative diagnosis of CNL.

MDS/MPN with thrombocytosis and SF3B1 mutation and myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis, NOS (Tables 16 and 17)

After the discovery that MDS/MPN-RS-T is frequently associ- ated with mutations in the spliceosome gene SF3B1 (which in turn are associated with the presence of ring sideroblasts), there is now sufficient evidence to support recognition of MDS/MPN associated with thrombocytosis and SF3B1 mutation. In the presence of SF3B1 mutation (.10% VAF), the identification of ring sideroblasts (although com- mon) is no longer required. The SF3B1 mutation is in most cases found in association with the JAK2 V617F mutation and much less commonly (in ,10% of cases) in association with the CALR or MPL W515 mutations. Although the pres- ence of comutation in 1 of these genes is not required for the diagnosis, their presence supports the diagnosis. For the rare cases of MDS/MPN with thrombocytosis and $15% ring sideroblasts that lack SF3B1 mutation, a designation of MDS/MPN-RS-T, NOS is appropriate. In addition, in line with the criteria for other MDS/MPN, the thrombocytosis and anemia for both MDS/MPN-T-SF3B1 and MDS/MPN-RS-T, NOS must both be present at the time of initial diagnosis. Cases of MDS- SF3B1 that later develop thrombocytosis are now considered to represent thrombocytotic progression of MDS-SF3B1.

MDS/MPN, NOS (Tables 18 and 19)

MDS/MPN, unclassifiable although largely a diagnosis of exclu- sion, is now better refined with the adoption of newly specified diagnostic requirements. These include a need for the presence of cytopenia in association with myeloproliferative features in PB and lack of specific gene rearrangements/fusions of M/LN-Eo with tyrosine kinase gene fusions. Establishment of clonality is expected, although the diagnosis can be made in the absence of clonality or mutations if there is histopathologic evidence of MDS/MPN and exclusion of other MDS/MPN entities. The new name of MDS/MPN, NOS was adopted in lieu of MDS/MPN-U because what was priorly “unclassifiable” has become now a disease entity and that this category should not be used to diag- nose (eg, advanced-stage MPN or triple negative MPN cases).

Premalignant clonal cytopenias and MDSs

CH represents the underpinning of MDS. Although CH has wide-reaching effects outside the hematopoietic system,[104] its association with ineffective hematopoiesis comprises the group of clonal cytopenias spanning from CCUS to MDS. Cytopenia in the context of clonal cytopenias is defined as the presence of acquired and sustained anemia (hemoglobin , 12 g/dL in females and , 13 g/dL in males), neutropenia (absolute neutro-phil count , 1.8 3 10^9/L), and/or thrombocytopenia (platelets , 150 3 10^9/L), that is not explained by another condition.[82]

Clonal cytopenia of undetermined significance (CCUS) and other pre-malignant clonal cytopenias (supplemental Table 4)

CH occurs when an expanded population of blood cells is derived from a single clone and is identified by the detection of somatic mutations or cytogenetic aberrations or copy number abnormalities on genetic testing. CHIP is defined by the pres- ence of a somatic mutation in a myeloid neoplasm driver gene (at VAF $ 2%) or a non–MDS-defining clonal cytogenetic aber- ration in a patient lacking a myeloid neoplasm or unexplained cytopenia. Both cytopenia and CHIP increase with age and are relatively common in elderly individuals. In CCUS, the cytopenia is persistent (4 months or longer in duration), idiopathic, and not caused by another comorbid condition, which must be carefully excluded.[105] Clonal cytopenia also characterizes paroxysmal nocturnal hemoglobinuria and a subset of aplastic anemia, both of which may progress to MDS.[106] Clonal cytopenia cases with monocytosis are considered to represent CMUS, because they have different progression patterns from CCUS (see above).[97] CCUS and other premalignant clonal cytopenias are distin- guished from MDS by lack of dysplasia or increased blasts on PB and BM examination. A threshold VAF of $2% is recom- mended for CCUS and other premalignant clonal cytopenias, recognizing that certain mutations and high VAF are associated with higher risk of progression to MDS.[107] Further study is war- ranted to better define high-risk CCUS and its relationship to bona fide MDS.[97,108] CH may also be detected in patients fol- lowing treatment for a myeloid neoplasm (most commonly AML) or a solid tumor, and in such cases, the clinical and biological implications may be different from CHIP or CCUS occurring in patients lacking a history of myeloid neoplasia.[109] VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syn- drome is a unique autoinflammatory syndrome associated with anemia and CH caused by somatic mutation in the UBA1 gene.[110] Because of its multisystem features, it is recommended to keep VEXAS separate from MDS, unless morphologic criteria of MDS are met (typically in the setting of acquired additional genetic aberrations).

MDS definition

MDSs are clonal hematopoietic neoplasms characterized by the combination of persistent unexplained cytopenia(s) and morpho- logic dysplasia and a propensity to progress to BM failure or AML. Although there is no formal requirement that the cytope- nia persist for a specific duration of time, in general, there should be clinical evidence that the blood count abnormality is chronic in duration (typically 4 months or longer) and is not explained by a drug, toxin, or comorbid condition. The thresh- old for defining dysplasia is recommended as 10% for all line- ages; for megakaryocytes, micromegakaryocytes are the most specific indicator of MDS, and a higher threshold of dysplasia may be warranted when other types of dysmegakaryopoiesis are included.[111,112] All MDS cases are assumed to be clonal, and a somatic genetic aberration is identifiable on targeted NGS panels in approximately 90% and conventional karyotype in 50% of cases. In cases with no clonality proven by current testing methods, a diagnosis of MDS can still be made in the presence of qualifying dysplasia and persistent cytopenia.[113] Conversely, several genetic abnormalities in the context of per- sistent cytopenia are still considered to be MDS-defining irre- spective of dysplasia; these have been updated from the revised fourth edition WHO classification (Table 20). MDS in chil- dren and adolescents lack recurrent mutations in genes of epi- genetic regulation or RNA splicing known to expand clonal hematopoiesis in adults; instead, somatic aberrations in SETBP1, ASXL1, RUNX1, and RAS/MAPK pathway mutations define the genomic landscape.[114-116] In addition, most MDS cases in chil- dren have considerable hypocellularity of the BM.[117,118] Given its unique features, the entity known as refractory cytopenia of childhood (RCC) is included in a new section of pediatric disorders (see below). Just as in the prior classification, the presence of persistent leukocytosis (WBC $ 13.0 3 10 /L, not explained by clonal lym- phocytosis or another comorbid condition), thrombocytosis (platelets $ 450 3 10^9/L, except in cases meeting criteria for MDS with del(5q) or with inv(3q)/t(3;3) cytogenetic aberrations), or monocytosis (monocytes $ 10% of leukocytes and absolute monocyte count $ 0.5 3 10^9/L) at the time of initial diagnosis excludes MDS and warrant classification as MDS/MPN or MPN.

MDS classification: subtypes without excess blasts

Recent studies have shown that in MDS without excess blasts, SF3B1 mutation defines a more homogeneous group than ring sideroblasts.[101] For this reason, the prior entity of MDS with ring sideroblasts (MDS-RS) has been replaced by MDS with SF3B1 mutation (MDS-SF3B1; Table 20). SF3B1-unmutated MDS-RS cases have clinical features and outcomes similar to MDS with single or multilineage dysplasia and are now classified as MDS, NOS, irrespective of the number of RS. Genetic risk stratification appears to supersede any effect of single vs multilineage dyspla- sia on the prognosis of lower risk MDS, but these are currently retained as subtypes of MDS, NOS.[101] MDS with isolated del(5q) has been retained with no changes from the revised fourth edition WHO classification, although the name has been simplified to MDS with del(5q), with the understanding that the del(5q) must be isolated or accompanied by only one other cytogenetic aberration except for 27 or del(7q). A new genetic subtype of MDS has been introduced, defined by the presence of multihit TP53 mutations,[119,120] and is discussed below. The prior category of MDS, unclassifiable (MDS-U) has been eliminated. Aside from del(5q), 27/del(7q), or a complex karyo- type, the previous MDS-defining cytogenetic abnormalities in cytopenic patients lacking dysplasia are now considered as CCUS. Cytopenic cases with del(5q), multihit TP53 mutation, or 27/del(7q) or complex karyotype that lack dysplasia or excess blasts are classified as MDS with del(5q), MDS with mutated TP53, or MDS, NOS. Although present in most cases, neither dysplasia nor ring sideroblasts are required to diagnose MDS- SF3B1. The MDS-U subtype with single lineage dysplasia and pancytopenia is no longer relevant, because cytopenias are already incorporated into the Revised International Prognostic Scoring System for MDS.[121] The presence of 1% PB blasts on 1 occasion is acceptable in any nonexcess blast MDS subtype; however, these patients should be followed closely and classi- fied as MDS with excess blasts if PB blasts of 1% are confirmed on another occasion, or reach 2% or higher.[122] The classification of lower-risk MDS has thus been simplified into 3 subtypes: 2 defined mainly by genetic features (SF3B1 mutation and del(5q)) and the remainder in MDS, NOS. Although there is poor reproducibility in distinguishing single lineage vs multilineage dysplasia in MDS,[123] this distinction has been retained in the subclassification of MDS, NOS. In the near future, genetic clustering analysis will likely aid in establishing additional genetic subgroups within MDS-NOS.[124,125]

MDS with excess blasts

MDS with excess blasts (MDS-EB) is separated from lower risk MDS subtypes by the presence of at least 5% myeloid blasts in the BM or at least 2% blasts in the PB (or 1% documented on 2 occasions; Table 20). With the introduction of the new MDS/AML category (discussed below), there is now only 1 MDS-EB subtype. The presence of excess blasts supersedes any of the above MDS subtypes, except for MDS with mutated TP53 (discussed below).

MDS/AML

Although the blast threshold of 20% defining AML remains, sev- eral additional genetic lesions are now considered to be defin- ing of AML for myeloid neoplasms with $10% BM or blood blasts (see AML section below). To acknowledge the biologic continuum between MDS and AML, the name of the previous category of MDS-EB2 in adults with 10% or more blasts is changed to MDS/AML, defined as a cytopenic myeloid neo- plasm and 10% to 19% blasts in the blood or BM. However, given their unique biological features and treatment approach, pediatric (age , 18 years) MDS-EB will continue to include patients with 10% to 19% blasts. Patients with MDS/AML should be eligible for both MDS and AML trials, which will facilitate optimizing the management of such patients. In the future, genetic features rather than an arbitrary blast cutoff may drive treatment decisions in this group.[126]

Myeloid neoplasms with mutated TP53 (Table 21) This disease category encompasses separate diagnoses of MDS,

MDS/AML, and AML with mutated TP53 (including pure ery- throid leukemia), according to the blast percentage. These dis- eases are grouped together because of their overall similar aggressive behavior irrespective of the blast percentage, war- ranting a more unified treatment strategy across the blast spec- trum.[120,127] The presence of multihit TP53 mutations in cytopenic myeloid neoplasms corresponds to a highly aggres- sive disease with short survival. Unlike other MDS, the prognosis of MDS with multihit TP53 does not appear to depend on the blast percentage, although multihit TP53 abnormalities appear to be more common in cases with increased blasts.[119,120] Multi- hit TP53 can be confirmed by the presence of 2 or more distinct TP53 mutations (VAF $ 10%) or a single TP53 mutation associ- ated with (1) a cytogenetic deletion involving the TP53 locus at 17p13.1; (2) a VAF of .50%; or (3) copy-neutral loss of heterozy- gosity (LOH) at the 17p TP53 locus.[119,127] In the absence of LOH information, the presence of a single TP53 mutation in the context of any complex karyotype is considered equiva- lent to a multihit TP53.[119,127] Complex karyotype alone in the absence of a TP53 mutation (even in the presence of 17p deletion) does not qualify for this category, as these cases have superior prognosis to TP53-mutated MDS.[120,128] Mono- allelic TP53 mutations in MDS have a less adverse effect on prognosis and different biology from cases with multihit TP53, and are not included in the MDS entity.[119] However, mono- allelic mutated TP53 AML has a poor prognosis, and thus monoallelic somatic mutations are allowed in MDS/AML and AML with mutated TP53.[127]

Patterns of progression in clonal cytopenias

The premalignant clonal cytopenias CCUS, aplastic anemia (AA), paroxysmal nocturnal hemoglobinuria (PNH), and VEXAS can progress to MDS once dysplasia, excess blasts, or MDS-defining genetic lesions occur. In the setting of a germline predisposition condition, progression to MDS follows different criteria and is discussed in the Pediatric and/or Germline Mutation-Associated Disorders section. Any nonexcess blast MDS subtypes may progress to MDS-EB, MDS/AML, or AML and similarly, MDS-EB may progress to MDS/AML or AML. These progression events should be documented in the pathology report. MDS may also progress to MDS, MDS/AML, or AML (depending on the blast count) with mutated TP53 with the acquisition of TP53 mutations and should be designated as such if a TP53 mutation develops later in the course of disease. Unlike the prior classification, cases of MDS with SF3B1 mutation that later develop thrombo- cytosis (with or without a JAK2 mutation) are no longer reclassi- fied as MDS/MPN. Similarly, the development of leukocytosis, thrombocytosis, or monocytosis in an established MDS case generally does not warrant reclassification as MDS/MPN. Such cases can be designated as MDS (and subtyped) with neu- trophilic, thrombocytotic, or monocytic progression. However, cases resembling bona fide CMML or, rarely, aCML, may rarely develop in patients previously diagnosed with MDS.

Further study is needed to distinguish between MDS progres- sion and true conversion to an MDS/MPN disease in these instances.[129-131]

Diagnostic qualifiers

All MDS cases that are therapy related should be qualified as such by entering a “therapy-related” statement after the diag- nosis. Although it remains important to recognize therapy-relatedness of myeloid neoplasms, the first priority is to classify the disease according to its morphologic and genetic fea- tures.[132] As CCUS and CHIP can occur as a consequence of cytotoxic therapy and are a precursor to therapy-related MDS and AML,[133] it is recommended to also qualify a diagnosis of CHIP and non-MDS clonal cytopenias as therapy related if they follow marrow exposure to chemotherapy or radiation therapy. Any underlying germline predisposition mutation or syndrome should also be specified as a qualifier after the MDS diagnosis and subtype (see further discussion on qualifiers in the AML sec- tion below).

Pediatric disorders and/or germline mutation-associated disorders

Although virtually any of the disorders in the ICC can occur in children, some are unique to childhood, and some are associated with germline genetic predisposition. Disorders arising from germline abnormalities, however, often present in adulthood. Because of the unique and overlapping fea- tures of these disorders, they are presented together in the classification.

JMML and related disorders (Tables 22 and 23; supplemental Table 5)

JMML is a unique clonal disorder of childhood characterized by constitutive activation of the RAS signal transduction pathway that was previously considered an MDS/MPN. Nearly all patients harbor mutations in the RAS pathway that define genetic and clinical subgroups. The ICC refines JMML as a genetic entity with the presence of molecular alteration of 1 of these RAS pathway genes as requirement for diagnosis. The diagnostic cri- teria for JMML are listed in Table 22. It is noted that approxi- mately 7% of cases may not meet the criteria for monocytosis listed in the table and approximately 3% will not demonstrate splenomegaly at presentation. Correlation with more detailed clinical features is needed in such cases.[134] The frequency of signs and symptoms of JMML are summarized in supplemental Table 5. JMML typically presents in early childhood with marked hepatosplenomegaly, lymphadenopathy, interstitial lung disease, and skin rash. Most cases show leukocytosis and leu- koerythroblastosis associated with monocytosis (monocyte count . 1 3 10^9/L).[134] Blasts and promonocytes account for ,20% of white blood cells in PB and nucleated cells in BM. JMML pathobiology is characterized by constitutive activation of the RAS signal transduction pathway. Canonical RAS pathway mutations in the PTPN11, NRAS, KRAS, NF1, CBL, and rarely RRAS genes are present in leukemic cells of more than 95% of patients and define genetically and clinically distinct sub- types.[135,136] Two subtypes are defined by germline events in either NF1 or CBL, which progress to malignancy with acquired biallelic inactivation of the respective genes in hematopoietic cells. The other subtypes, PTPN11-, NRAS-, and KRAS-mutated JMML, are characterized by heterozygous, somatic gain-of-function mutations in children without germ- line disease. KRAS- and NRAS- mutated JMMLs with a normal karyotype share overlapping features with a rare disorder called RAS-associated autoimmune leukoproliferative disor- der, which may represent different phenotypes of the same disorder.[137] Clonal disease that phenotypically mimics JMML but does not harbor 1 of these RAS pathway mutations is classified as JMML- like neoplasm.

Noonan syndrome–associated myeloproliferative disorder, a transient disease thought to be of polyclonal origin, can in its severe form clinically resemble JMML. JMML-like neoplasms Cases in nonsyndromic patients that phenotypically resemble JMML but lack a RAS pathway mutation are referred to as JMML-like in the ICC (Table 23). This group includes JMML mimics with rare rearrangements, like ALK,[138,139] ROS1,[139] FIP1L1::RARA,[140,141] or CCDC88C::FLT3[142,143] fusions. Disorders with AML-defining recurrent genetic aberrations or M/ LN-eo associated with tyrosine kinase gene fusions are excluded from JMML-like neoplasms.

Noonan syndrome–associated myeloproliferative disorder

Patients with Noonan syndrome and germline mutations in PTPN11, KRAS, NRAS, or RIT1 can experience a transient mye- loproliferative disorder in the first year of life.[135] Although this disorder may be indistinguishable from JMML by clinical and hematologic parameters, acquired somatic mutations are con- spicuously absent.[144]

Refractory cytopenia of childhood (Box 1)

RCC represents a well-recognized type of BM failure seen in children. Both persistent cytopenia and evidence of dysplasia are required for its diagnosis. Because of the marked BM hypo- cellularity found in $80% of children with RCC, its recognition requires BM biopsy examination to identify its characteristic his- topathologic appearance.[145] The diagnostic criteria described in the revised fourth edition WHO have now been updated (Box 1). It has become evident that only in a proportion of cases diagnosed as RCC can acquired somatic mutations or cytoge- netic abnormalities be identified.[146] In others, a germline predisposition may have been present that preceded the evolution to RCC. These conditions include Fanconi anemia,[147] dyskeratosis congenita, Shwachman-Diamond syndrome,[148] GATA2 defi- ciency,[149] and SAMD9/SAMD9L syndromes.[150] In these settings, RCC represents progression to BM failure or frank MDS. Although it is apparent that not all RCC cases are bona fide MDS, monosomy 7 and del(7q) are the most frequent MDS-defining genetic abnormalities.[118,151] Recent insight into karyotype instability and somatic rescue mechanisms[150,152,153] demonstrated, however, great plasticity of hematopoiesis in young patients. Risk-based treatment strategies for children with RCC must account for this heterogeneity.

Hematologic neoplasms with germline predisposition (Table 24)

The identification of hematologic neoplasms with germline mutations is critical for proper diagnosis, patient management, screening of related donors for stem cell transplantation, selec- tion of therapeutic conditioning, and genetic counseling for affected family members. A high index of suspicion of germline mutation is important particularly for younger patients diag- nosed with hematologic neoplasms and for patients that will be transplanted using related donors. The unwitting use of related transplant donors who harbor the same germline mutation as the patient has led to donor-derived MDS and AML and poor outcomes, underscoring the need for increased awareness and recognition of hematologic neoplasms with germline predisposition.[154-157]

The ICC of hematologic neoplasms with germline predisposition includes 4 major subgroupings (Table 24) with new entities added in comparison with the 2016 WHO classification. Increas- ing data have demonstrated that many genes in the prior classification predispose not only to myeloid malignancy but also to lymphoid malignancy. Hence, the title is changed from “myeloid neoplasms” to “hematologic neoplasms” with germline predis- position. Several genes have emerged with substantial data doc- umenting germline predisposition to hematologic malignancy that warranted incorporation into the new ICC (including SAMD9, SAMD9L, IKZF1, PAX5, and TP53). Any underlying germline predisposition mutation or syndrome should also be specified as a qualifier after the MDS, AML, or other malignancy diagnosis and subtype.

Hematologic neoplasms with germline predisposition without a constitutional disorder The genes in this group include CEBPA, which predisposes to AML, and DDX41, which predisposes to both myeloid and lym- phoid neoplasms. TP53 is added, recognizing the importance of Li-Fraumeni syndrome and predisposition to myeloid and lym- phoid malignancies in both treatment-naive and therapy-related settings.[158-162]

Hematologic neoplasms with germline predisposition associated with a constitutional platelet disorder

The genes in this group have not changed and include RUNX1, ANKRD26, and ETV6. It is noted that morphologic megakaryo- cytic dysplasia is common in the BMs of these patients in the set- ting of isolated thrombocytopenia and absence of MDS.[163,164] Lymphoid malignancies have been reported with germline RUNX1 or ETV6 in addition to myeloid neoplasia.

Hematologic neoplasms with germline predisposition associated with a constitutional disorder affecting multiple organ systems

Similar to the prior 2016 WHO classification, this group includes germline mutations in GATA2, germline mutations associated with classical BM failure disorders, germline mutations in RAS- pathway genes (NF1, PTPN11, CBL) associated with neurofibromatosis, Noonan-like syndromes predisposing to JMML, and Down syndrome, which predisposes to both myeloid and lymphoid neoplasia. Additions to this group include SAMD9 and SAMD9L, which predispose to acquired monosomy 7/del(7q) and MDS.[116,150,165]

ALL with germline predisposition

Germline mutations of IKZF1[166] and PAX5[167,168] are both associ- ated with predisposition to ALL. These germline mutations also predispose to loss of B-cell subsets and immune deficiency. Down syndrome and germline mutations in ETV6 and TP53 (Li-Fraumeni syndrome) also predispose to ALL and myeloid malignancies.

Other germline mutations

Other germline mutations also result in predisposition to hemato- logic malignancies, including Bloom syndrome (BLM),[169] ataxia- telangiectasia, Nijmegen breakage syndrome, Noonan syndrome, constitutional mismatch repair deficiency syndrome,[170,171] and germline mutations in DNMT3A,[172] ERCC6L2,[173] MBD4,[174] and XPC.[175] Limited cases of hematologic malignancies have been reported for germline genetic mutations in CSF3R,[176] MECOM,[177] SRP72,[178] and TET2.[179,180]

Diagnosis of MDS in the setting of germline predisposition

The ICC recognizes that many of the genes predisposing to myeloid malignancy also predispose to baseline changes in BM cells that overlap with dysplastic features. These dyspoietic changes may be present irrespective of whether the patient has a myeloid malignancy. For this reason, a germline predisposition should be considered for cases with morphologic atypia in the absence of additional factors supporting a diagnosis of MDS or other myeloid malignancy. In general, the development of MDS in patients with germline predisposition is associated with new or progressive cytopenia(s) often in the setting of rising marrow cellularity, overt multilineage dysplasia, increased blasts, and/or acquired pathogenic genetic alterations. Emergence of del(5q), 27/del(7q), complex karyotype, multihit TP53 mutations (VAF . 10%), or SF3B1 mutation (VAF . 10%) is considered MDS defin- ing. Acquired genetic changes must be interpreted in the con- text of the specific germline genetic mutation: for example, patients with Shwachman Diamond syndrome frequently develop small stable clones with monoallelic TP53 mutations, and in isolation, these are not considered to represent develop- ment of MDS; however, biallelic TP53 mutations in this context are associated with myeloid malignancy.[181]

Acute myeloid leukemia (Tables 25 and 26; supplemental Table 6)

AML represents a heterogenous group of genetically distinct disorders. The updated classification retains many of the previ- ously defined AML types with recurrent genetic abnormalities and includes other genetically related entities (Table 25; supple- mental Table 6) to move to a more genetically defined classifica- tion. Although the importance of prior therapy, antecedent myeloid neoplasms (ie, MDS or MDS/MPN), or underlying germ- line genetic disorders predisposing to the development of AML is well recognized, the classification now identifies such associa- tions as qualifiers to the diagnosis rather than as specific disease categories (Table 26) in an attempt to reduce confusion caused by the substantial overlap of prior AML categories. Using this approach, the prior stand-alone categories of therapy-related myeloid neoplasms and AML with myelodysplasia-related changes are eliminated. The ICC AML categories are listed in Table 25, with several key differences from prior classifications. The prior category of AML with myelodysplasia-related changes (AML-MRC) was an attempt to identify patients with a worse prognosis compared with AML, NOS.[5,8,182] Although the identi- fication of multilineage dysplasia was a crude proxy for underly- ing myelodysplasia-related cytogenetic abnormalities, the association of multilineage dysplasia in a subset of patients with low-risk gene mutations, especially NPM1 or biallelic CEBPA,[183-185] highlighted the need for molecular refinement of that category. Additionally, overlapping features between AML with myelodysplasia-related changes and therapy-related AML occur, further identifying a need for a better-defined approach to AML classification.

AML with mutated TP53 is now recognized as a separate entity within the group of myeloid neoplasms with mutated TP53 (which also includes MDS and MDS/AML with mutated TP53, discussed above and in Table 21). Like MDS, AML with mutated TP53 is typically associated with complex cytoge- netic abnormalities and with a very poor out- come.[120,127,186-188] Additionally, a panel of genes has been identified to be strongly associated with secondary AML aris- ing from prior myeloid neoplasia.[187,189-193] Both categories were previously identified as AML genomic classes (TP53/ chromosomal aneuploidy-complex karyotypes with abnormali- ties of chromosomes 5 and/or 7, often called monosomal kar- yotypes and chromatin/spliceosome, respectively).[187] The myelodysplasia-related mutations confer a similarly adverse prognosis to cases presenting as de novo AML that would previously fall into the category of AML, NOS. Based on these findings, the category of AML-MRC is eliminated while retaining a category of AML with myelodysplasia-related cyto- genetic abnormalities and with new categories of AML with mutated TP53 and AML with myelodysplasia-related gene mutations. TP53 mutations define a distinctly aggressive AML category, whether they present de novo, as progression of MDS, or as therapy-related disease. Although multihit TP53 mutation is required for MDS with mutated TP53, in AML and MDS/AML with mutated TP53, any pathogenic TP53 mutation VAF of .10% is sufficient.[119,120,127] Mutations of ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2 qualify for a diagnosis of AML with myelodysplasia- related gene mutations (now encompassing the prior provi- sional entity of AML with mutated RUNX1). Finally, in the absence of a myelodysplasia-related gene mutation, TP53 mutation, or other recurring genetic abnormalities definitional of specific AML categories, a case may be diagnosed as AML with myelodysplasia-related cytogenetic abnormalities based on specific karyotype findings. The WHO fourth edition and revised fourth edition classifica- tions included 3 specific categories of AML (other than pure erythroid leukemia) that defined AML without regard to myeloblast percentage in the appropriate clinical setting: AML with t(8;21)(q22;q22.1)/RUNX1::RUNX1T1, AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11, and acute promyelocytic leukemia with t(15;17)(q24;q21)/ PML::RARA. Cases in these categories diagnosed with very low blast counts (,20%) are uncommon. The ICC expands the categories that may be diagnosed as AML with ,20% blasts to encompass additional recurring genetic abnormali- ties (including gene mutations),[194-203] with at least 10% blasts (or so-called “blast equivalents” including promonocytes and neoplastic promyelocytes in the appropriate pathologic set- ting) in the blood or marrow for such a diagnosis. The remaining AML categories retain the 20% or more blast requirement. MDS cases with 10% to 19% blasts are now diagnosed as MDS/AML, as described above, reflecting the diagnostic continuum between AML and MDS and clinical and genetic heterogeneity among individual patients with these lower blast counts.[126,204-207] Cases of MDS/AML are subclassified as MDS/AML with mutated TP53, MDS/AML with myelodysplasia-related gene mutations, MDS/AML with myelodysplasia-related cytogenetic abnormalities, or MDS/ AML, NOS. Several prior AML-related disease categories, including mye- loid sarcoma, myeloid neoplasms associated with Down syn- drome, and blastic plasmacytoid dendritic cell neoplasm are unchanged. Changes to acute leukemias of ambiguous line- age were not addressed in the CAC, but an ICC working group will report on them separately in the future. One signif- icant change, however, relates to the prior category of AML with biallelic mutations of CEBPA. Several studies now dem- onstrate it is the presence of in-frame bZIP mutations of CEBPA that define the prognostic entity with a unique gene expression profile,[208-210] and this favorable category is now updated to include this abnormality, without the requirement of biallelicmutations. The hierarchy of disease categories generally follows the order of entities listed in Table 25. The traditional genetic disease groups named after a single abnormality rarely show overlap. Such rare occurrences should be viewed as exceptions and clearly identified. Although TP53 mutations may overlap with other categories, their presence is usually predictive of a worse prognosis and such a mutation should be noted with the other genetic abnormality. The single gene mutation or gene fusion categories take precedent over the myelodysplasia-related gene mutation and the myelodysplasia-related cytogenetic groups, although such findings, may again impact prognosis in the genetic groups and should be noted. After excluding all other genetic categories, some cases will remain unclassified and those will continue to be diagnosed as AML, NOS. Previously used morphologic or cytochemical subtypes of AML, NOS have limited prognostic significance, but pathologists may continue to subclassify such cases if desired. Of note, pure erythroid leu- kemia is typically associated with TP53 mutations, and these cases are now classified within the category of AML with TP53 mutations.

B-ALL, T-ALL (Tables 27 and 28; supplemental Table 7)

Synonym: B-(T-)lymphoblastic lymphoma/leukemia
The updated classification includes some revisions to entities previously present in the 2016 WHO classification and introdu- ces a number of new subtypes (Table 27). BCR::ABL1-

positive ALL from the prior classification is now divided into 2 biologi- cally distinct subsets, 1 of which appears more closely related to CML presenting in lymphoid blast phase.[211,212] These subsets cannot be distinguished by the use of p190 vs p210 fusion pro- teins, but rather can by fluorescence in situ hybridization (FISH), based on whether the translocation can be detected in granulo- cytes, indicating a multilineage BCR::ABL1 fusion, as opposed to a lymphoid-only rearrangement in which FISH is only positive in lymphoblasts.[211-213] In some cases, it may be necessary to sort cells to obtain enough myeloid cells to do this.[211] Further evidence comes from the finding that RT-PCR studies for BCR::ABL1 following treatment may show high level positivity when both flow cytometry and molecular MRD methods show no or little evidence of MRD.[212,214] Prognosis and optimal treat- ment of these 2 variants may also differ.[211] Cases of B-ALL, BCR::ABL1 like are now recognized as having a wide variety of genetic lesions including JAK-STAT alterations (including CRLF2-rearrangement, JAK fusions, and EPOR rearrangement, among others), ABL1 class fusions, and others, so that this entity has now been subdivided. It is particularly important to recognize those with ABL-class fusions because of their unique pattern of response to various ABL1-class tyrosine kinase inhibitors[215]; some other fusions, such as those involving NTRK, may also respond.[216] The most common alteration in the JAK-STAT category is a CRLF2 rearrangement, which in many cases can be detected by FISH (or screened by CRLF2 flow cytometry as CRLF2 is upregulated). CRLF2 rearrangement is accompanied by JAK mutations in approximately half of cases, with other kinase activating mutations in additional cases, resulting in acti- vation of JAK-STAT signaling. Responsiveness to approved JAK inhibitors such as ruxolitinib is variable in preclinical models and is being formally evaluated in clinical trials.

Table 28 lists new subcategories of ALL with driver structural lesions, commonly also recognizable by their distinct gene expression signatures. Several have translocations most readily detected by whole transcriptome sequencing, although nonse- quencing approaches using RT-PCR or commercially available FISH probes are possible for many of these. A few entities are defined by mutations resulting in single amino acid substitutions.

B-ALL with MYC rearrangement In contrast to Burkitt or other MYC-rearranged lymphomas, these have an immature phenotype, generally positive for terminal deoxynucleotidyl transferase (TdT), although not CD34, and often are negative or partly positive for CD20. Surface immunoglobulin may be posi- tive.[217] Some resemble Burkitt lymphoma morphologically. There may be accompanying BCL2 and less commonly BCL6 translocations.[218] These cases mostly have a leukemic rather than lymphomatous presentation. Cases of aggressive B-cell lymphomas may sometimes express TdT and have other pheno- typic markers of immaturity, and follicular lymphomas may undergo lymphoblastic transformation[219,220]; such cases should be classified under the appropriate lymphoma rather than in this category. These high-grade, but TdT1 (usually partial), lymphomas may have MYC or even “double hit” rearrangements, but have a different mutational profile from B-ALL with MYC rear- rangement[220] and show evidence of somatic hypermutation, whereas B-ALL with MYC rearrangements have unmutated immunoglobulin V(H) genes.[217]

New ALL entities defined by translocations DUX4 is most com- monly rearranged to IGH, and the IGH::DUX4 translocation is typically cryptic because of the repetitive, duplicated nature of the DUX4 locus and the rearrangement to IGH enhancers. DUX4-rearranged ALL is relatively common in children and asso- ciated with excellent prognosis in both children and adults, even when associated with other poor risk features, including IKZF1 deletion.[221-223] Detection by FISH is difficult, but overexpression of DUX4 is specific and can be detected by quantitation of DUX4 gene expression or immunohistochemistry[224]; expression of CD371 is associated with DUX4 rearrangement and may be identified by flow cytometry.[225] MEF2D-rearranged B-ALL has a poor prognosis. Cases with the common 3^9 BCL9 fusion partner can be detected with available fusion FISH probes, and cases can be suspected based on a CD10-/dim, CD381, cm1 immu- nophenotype.[226,227] The mechanism of leukemogenesis, involv- ing deregulation of the MEF2D target gene HDAC9, may sensitize cells to histone deacetylase (HDAC) inhibitors.[226] ZNF384-rearranged leukemia represents a distinct entity with characteristic gene expression profile, lineage ambiguity, and patterns of concomitant mutation that may manifest as B-ALL (often with aberrant myeloid antigen expression insufficient to result in classification as MPAL) or B/myeloid MPAL.[228] Shift in lineage during disease evolution is common and further supports ZNF384 rearrangement defining a distinct entity irrespec- tive of initial immunophenotype. ZNF384 is rearranged to a diverse range of fusion partners, commonly EP300, TCF3, and TAF15. Additional cases have a similar gene expression profile but harbor rearrangement of ZNF362. Both leukemias typically lack expression of CD10, as well as having variable expression of myeloid antigens, with expression of MPO often distinguish- ing B-ALL (MPO negative) from B/myeloid MPAL (MPO posi- tive).[229-232] Prognosis varies with fusion partner, with EP300 having the best prognosis and TCF3 the worst.[233] NUTM1-rear- ranged leukemia is rare and most common in infants that lack KMT2A rearrangements but has a much more favorable progno- sis than KMT2A-R leukemias.[234] It can be diagnosed using stan- dard NUTM1 breakapart FISH probe set.[235] TCF3/4::HLF rearranged leukemia is exceptionally rare and probably only found in children; it has a very poor prognosis,[236] although anti- CD19 therapy and transplant has shown some promise.[237] CDX2/UBTF-deregulated B-ALL is characterized by 2 concomi- tant genomic alterations in all cases: a focal deletion on chromo- some 13 upstream of FLT3 that results in retargeting of the PAN3 enhancer and deregulation of CDX2 and a focal deletion of the 3^9 region of UBTF that results in expression of the chime- ric UBTF::ATXN7L3 fusion oncoprotein.[238-240] This leukemia is most common in female adolescents and young adults and appears to have poor outcome if treated with conventional chemotherapy.

New ALL entities with point mutations Two uncommon entities with hotspot point mutations produce leukemias with unique gene expression patterns distinct from all other subtypes. IKZF1 N159Y is rare and produces a missense mutation leading to upregulation of several oncogenic genes.[222,241] PAX5 P80R[241,242] is more common, especially in adults and has a relatively favorable prognosis; leukemogenesis depends on biallelic alteration of PAX5, with either deletion of the wild- type allele or copy neutral loss of heterozygosity.[241]
Provisional entities (supplemental Table 7) Some cases are phenocopies of several of the subtypes described above and have identical gene expression profiles but lack the requisite structural lesion. Because these cannot yet as a rule be diag- nosed by methods other than gene expression profiling, they are considered provisional. ETV6::RUNX1-like B-ALL cases share the CD27^1 ,CD44 dim/neg phenotype of ETV6::RUNX1 B- ALL[223,243] and in pediatrics appear to have the same favorable prognosis.[244] A relatively large subtype is PAX5-altered B-ALL (PAX5alt), which is characterized by a variety of different altera- tions in PAX5, including rearrangements, point mutations, and intragenic lesions[241,245]; although many of these can be identi- fied directly, complete definition of the group requires gene expression profiling. Cases with the H1038R mutation in ZEB2 co-cluster with those with IGH::CEBPE[244] and have a poor prog- nosis,[246] but these lesions do not appear to define this group uniquely.

T-ALL

Early T precursor ALL (ETP ALL) ETP ALL is currently diag- nosed by immunophenotype, and the definition has not changed. It is now recognized that about a third of ETP ALL is characterized by rearrangement and deregulation of the T-lineage transcription factor gene BCL11B in hematopoietic stem cells.[247-249] More than 80% of cases have activating FLT3 mutations, with all cases exhibiting high FLT3 expression. Most cases may be detected by FISH to detect disruption of the BCL11B locus. Also, there are some cases of T-ALL that are phe- notypically similar to ETP except that CD5 is present on .75% rather than #75% of cells; these have been referred to as “near- ETP ALL” and have different genomic lesions from those of ETP, with some overlap,[250,251] and there are minor differences from ETP in clinical presentation and response to therapy.[251]

The remainder of T-ALL can be subclassified based on aberrant activation of different families of transcription factors (see reviews for detailed discussion),[251-259] although the underlying lesions are complex so that diagnosis is challenging, and sub- classification is not typically used in clinical trials. Moreover, there is some variability in how different authors define different subtypes.[252,255,258] For these reasons they are considered provi- sional entities in this classification.

Authorship

Contribution: D.A.A., A.O., R.P.H., M.J.B., K.R.C., H.-M.K., S.A.W., M.C., H.D., and A.T. oversaw the project and wrote the manuscript. All other authors participated in the clinical advisory committee meeting to draft the classification and reviewed and edited the final manuscript.

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