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Myelodysplastic/myeloproliferative neoplasms

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The myelodysplastic/myeloproliferative neoplasms (MDS/MPN) include clonal myeloid neoplasms that overlap the MDS and MPN categories and at the time of initial diagnosis exhibit some clinical, laboratory, or morphologic features supporting the diagnosis of myelodysplastic syndrome (MDS) and at the same time show proliferative features in keeping with the diagnosis of a myeloproliferative neoplasm (MPN). Although the clinical, morphologic, and laboratory findings vary along a continuum from MDS to MPN, distinctive features are usually present that allow assignment of most of the cases to 1 of 3 distinct subtypes recognized by the 2008 World Health Organization (WHO) classification: chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia, *BCR-ABL*$^-$(aCML, *BCR-ABL1*$^-$), and juvenile myelomonocytic leukemia (JMML). The WHO classification also recognizes a provisional category of the MDS/MPN, unclassifiable (MDS/MPN, U), including the provisional entity of refractory anemia with ring sideroblasts and thrombocytosis (RARS-T). In the past 2 to 3 years since the publication of the WHO classification in 2008, dynamic progress in array technologies and next-generation amplicon deep sequencing has provided new insights into the molecular pathogenesis of MDS/MPN, especially CMML and JMML. In this review we will give an overview of these neoplasms and focus on adult MDS/MPN, especially CMML. We will give only brief updates for aCML and RARS-T; JMML will be discussed in a separate article.

The 2008 World Health Organization (WHO) classification introduced changes in the nomenclature and classification of the myeloid neoplasms that diverge from the 2001 3rd edition. Importantly, for the group of diseases discussed in this paper, the nomenclature has been changed from "myelodysplastic/myeloproliferative disorders" to "myelodysplastic/myeloproliferative neoplasm" (MDS/MPN) to underscore their neoplastic nature.[1] The MDS/MPN subgroup includes clonal myeloid neoplasms that at the time of initial diagnosis exhibit some clinical, laboratory, or morphologic features supporting the diagnosis of a myelodysplastic syndrome (MDS), such as persistent cytopenia(s) and dysplasia involving 1 or more of the myeloid lineages. At the same time, however, they show proliferative features, such as neutrophilia, monocytosis, and/or thrombocytosis, often with accompanying splenomegaly, which are more in keeping with the diagnosis of a myeloproliferative neoplasm (MPN). Thus, clinically, hematologically, and morphologically MDS/MPN overlap the MDS and MPN categories.[1,2] Cases that have a *BCR-ABL1* fusion gene or rearrangements of *PDGFRA, PDGFRB,* and *FGFR1* are excluded from the MDS/MPN category.

In most cases of MDS/MPN the bone marrow is hypercellular because of proliferation of at least 1 of the myeloid lineages. Blasts (including promonocytes, which are "blast equivalents") are less than 20% of the white blood cells (WBCs) in the peripheral blood and of the nucleated cells in the bone marrow at diagnosis. As is true for MDS and MPN, however, these neoplasms may progress to bone marrow failure or transform to acute myeloid leukemia (AML). Although the clinical, morphologic, and laboratory findings vary along a continuum from MDS to MPN, distinctive

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features are usually present that allow assignment of most of the cases to 1 of 3 distinct subtypes recognized by the 2008 WHO classification: chronic myelomonocytic leukemia (CMML),[3] atypical chronic myeloid leukemia, *BCR-ABL1*$^-$ (aCML, *BCR-ABL1*$^-$),[4] and juvenile myelomonocytic leukemia (JMML).[5] The WHO classification also recognizes a provisional category of the MDS/MPN, unclassifiable (MDS/MPN, U), including the provisional entity of refractory anemia with ring sideroblasts and thrombocytosis (RARS-T).[6]

In the past 2 to 3 years since the publication of the WHO classification in 2008, dynamic progress in array technologies and next-generation amplicon deep sequencing (NGS) has provided new insights into the molecular pathogenesis of MDS/MPN, especially CMML and JMML. In this review we will focus on adult MDS/MPN, especially CMML, and give only brief updates for aCML and RARS-T; JMML will be discussed in a separate article.

Etiology and pathogenesis of MDS/MPN

The etiology of the MDS/MPN entities is unknown for most cases. A minority of cases are related to prior cytotoxic therapy and should be classified as therapy-related myeloid neoplasms. For the remaining cases, although there are no currently recognized cytogenetic or molecular genetic abnormalities specific for any MDS/MPN subtype, data are accumulating that suggest similar molecular defects and altered signal transduction pathways may be shared among them. In the past most attention was focused on point mutations of genes encoding proteins involved in the RAS/RAF/MAPK pathway of signal transduction. More recently, single nucleotide polymorphism array karyotyping, array-comparative genomic hybridization, and direct sequencing of candidate genes with sensitive NGS technologies have uncovered an unexpectedly high frequency of uniparental disomy in MDS/MPN and have identified recurrent alterations of genes heretofore not suspected to be involved in these neoplasms, specifically *RUNX1*, *TET2*, *CBL*, *ASXL1*, *EZH2*, and *IDH1/IDH2*.[7-26] These technologies have dramatically increased the incidence of genetic abnormalities detected in MDS/MPN. For example, in 1 study of a cohort of 81 CMML cases, only 15 (18.5%) remained in which no mutation was detectable. In total, 81.5% of cases harbored at least 1 molecular aberration of 11 of the 12 candidate genes analyzed (*EZH2, TET2, ASXL1, CBL, NRAS, KRAS, JAK2, RUNX1, IDH1, IDH2, NPM1,* and *MPL*).[16]

Some of these recently identified mutations are associated with specific morphologic features of MDS/MPN, such as monocytosis (*TET2, CBL*), proliferative phenotype (RAS), or disease progression/adverse prognosis (*RUNX1, ASXL1,* and *EZH2*). Although detailed molecular characterization of these mutations in a clinical setting is difficult, at least at this time, they provide important insights into the molecular pathogenesis and biology of this group of diseases and provide information for potential therapeutic targets. This information may ultimately lead, in the future, to a newly refined classification of MDS/MPN.

CMML

The criteria for CMML are presented in Table 1. Monocytosis ($>1.0 \times 10^9$/L) with monocytes accounting for 10% or more of the peripheral blood WBCs is the major defining feature of CMML. Although absolute monocytosis in the blood is re-

Table 1 WHO diagnostic criteria for chronic myelomonocytic leukemia[3]

1. Persistent peripheral blood monocytosis $>1 \times 10^9$/L
2. No Philadelphia chromosome or *BCR-ABL1* fusion gene
3. No rearrangement of *PDGFRA* or *PDGFRB* (should be specifically excluded in cases with eosinophilia)
4. Fewer than 20% of blasts* in the peripheral blood and in the bone marrow
5. Dysplasia in 1 or more myeloid lineages. If myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if the other requirements are met and
   - -an acquired, clonal cytogenetic, or molecular genetic abnormality is present in hemopoietic cells or
   - -the monocytosis has persisted for at least 3 months and
   - -other causes of monocytosis have been excluded

–Blasts include myeloblasts, monoblasts, and promonocytes. Abnormal monocytes that can be present both in the peripheral blood and in the bone marrow are excluded from the blast count.

CMML-1

–Blasts (including promonocytes) <5% in the peripheral blood and <10% in bone marrow

CMML-2

–Blasts (including promonocytes) 5% to 19% in peripheral blood or 10% to 19% in the bone marrow or when Auer rods are present, irrespective of the blast plus promonocyte count

Additional information: Difficult at times to distinguish promonocytes from abnormal monocytes. Promonocytes have light gray or slightly basophilic cytoplasm with a few scattered, fine lilac-colored granules, finely distributed, stippled nuclear chromatin, variable prominent nucleoli, and delicate nuclear folding or creasing (WHO, 2008). Abnormal monocytes have more condensed chromatin, abnormally shaped, irregular, or folded nuclei, and abundant grayish blue cytoplasm, with more cytoplasmic granules and often more cytoplasmic vacuoles.

Monocytic precursors may be also difficult to distinguish from granulocytic precursors. Nonspecific esterase staining in peripheral blood and bone marrow may be helpful.

Cytogenetic abnormalities: The most frequent single chromosomal abnormality in CMML is trisomy 8, followed by monosomy 7 and other abnormalities, including -5, -7, del (12p), del (20q), i(17), and complex karyotype.[2,3,30,55]

Molecular genetic: *NRAS* or *KRAS, RUNX1, TET2, CBL, ASXL1* mutated in 20% to 60%,[7,8,10-12,14,15,17,20,21,30,57,59,60] less commonly *EZH2* (11%-13%),[16,22,23] *IDH1/IDH2, JAK2, NPM1*(less than 10%),[9,16,21,25,77-79,83] and infrequent *FLT3, CEBP, WT1,* and *PTPN11* mutations.[7,9,59,60]

TET2 and *CBL* mutations are mainly associated with monocytic proliferation,[11,12] *RAS* and *JAK2* with proliferative phenotype,[7,61,77-79] and *RUNX1, ASXL1,* and *EZH2* with disease progression and/or adverse clinical outcome.[8,20,21,23]