leukocytosis, transfusion requirement, and increased immature cells in the peripheral blood. Conventional chemotherapy is largely ineffective in the treatment of aCML. However, a favorable experience with ASCT was reported in nine patients; after a median follow-up of 55 months, the majority of the patients remained in complete remission.

CHRONIC MYELOMONOCYTIC LEUKEMIA

Chronic myelomonocytic leukemia (CMML) is classified under the WHO category of MDS/MPN and is defined by an absolute monocyte count (AMC) of >1 × 10^9/L in the peripheral blood. Median age at diagnosis ranges between 65 and 75 years, and there is a 2:1 male predominance. Clinical presentation is variable and depends on whether the disease presents with MDS-like or MPN-like phenotype; the former is associated with cytopenias and the latter with splenomegaly and features of myeloproliferation such as fatigue, night sweats, weight loss, and cachexia. About 20% of patients with CMML experience serositis involving the joints (arthritis), pericardium (pericarditis and pericardial effusion), pleura (pleural effusion), or peritoneum (ascites).

Pathogenesis Clonal cytogenetic abnormalities are seen in about one-third of patients with CMML and include trisomy 8 and abnormalities of chromosome 7. Almost all patients with CMML harbor somatic mutations involving epigenetic regulator genes (e.g., *ASXL1, TET2*), spliceosome pathway genes (e.g., *SRSF2*), DNA damage response genes (e.g., *TP53*), and tyrosine kinases/transcription factors (e.g., *KRAS, NRAS, CBL,* and *RUNX1*). However, none of these mutations are specific to CMML, and their precise pathogenetic contribution is unclear.

Diagnosis Reactive monocytosis is uncommon but has been reported in association with certain infections and inflammatory conditions. Clonal (i.e., neoplastic) monocytosis defines CMML but is also seen with juvenile myelomonocytic leukemia and acute myeloid leukemia with monocytic differentiation. The WHO diagnostic criteria for CMML are listed in Table 135e-5 and include persistent AMC >1 × 10^9/L, absence of *BCR-ABL1*, absence of the *PDGFRA* or *PDGFRB* mutations, <20% blasts and promonocytes in the peripheral blood and bone marrow, and dysplasia involving one or more myeloid lineages.

The bone marrow in CMML is hypercellular with granulocytic and monocytic proliferation. Dysplasia is often present and may involve one, two, or all myeloid lineages. On immunophenotyping, the abnormal cells often express myelomonocytic antigens such as CD13 and CD33, with variable expression of CD14, CD68, CD64, and CD163. Monocytic-derived cells are almost always positive for the cytochemical nonspecific esterases (e.g., butyrate esterase), whereas normal granulocytic precursors are positive for lysozyme and chloroacetate esterase. In CMML, it is common to have a hybrid cytochemical staining pattern with cells expressing both chloroacetate and butyrate esterases simultaneously (dual esterase staining).

Prognosis A meta-analysis showed median survival of 1.5 years in CMML. Numerous prognostic systems have attempted to better define and stratify the natural history of CMML. One of these, the Mayo prognostic model, assigns one point each to the following four independent prognostic variables: AMC >10 × 10^9/L, presence of circulating immature cells, hemoglobin <10 g/dL, and platelet count <100,000/mL. This model stratified patients into three risk groups: low (0 points), intermediate (1 point), and high (≥2 points), translating to median survival times of 32, 18, and 10 months, respectively.

A French study incorporated *ASXL1* mutational status in 312 CMML patients. In a multivariable model, independent predictors of poor survival were WBC >15 × 10^9/L (3 points), *ASXL1* mutations (2 points), age >65 years (2 points), platelet count <100,000/mL (2 points), and hemoglobin <10 g/dL in females and <11 g/dL in males (2 points). This model stratified patients into three groups: low (0–4 points), intermediate (5–7 points), and high risk (8–12 points), with median survival times of not reached, 38.5 months, and 14.4 months, respectively.

Treatment Current treatment consists of hydroxyurea and supportive care, including red cell transfusions and use of erythropoiesis-stimulating agents (ESAs). The value of hydroxyurea was reinforced by a randomized trial against oral etoposide. No other single or combination chemotherapy has been shown to be superior to hydroxyurea. ASCT is a viable treatment option for transplant-eligible patients with poor prognostic features. Given the MDS/MPN overlap phenotype and the presence of MDS-like genetic/methylation abnormalities in CMML, hypomethylating agents such as 5-azacitidine and decitabine have been used with limited efficacy.

JUVENILE MYELOMONOCYTIC LEUKEMIA

Juvenile myelomonocytic leukemia (JMML) is primarily a disease of early childhood and is included, along with CMML, in the MDS/MPN WHO category. Both CMML and JMML feature leukocytosis, monocytosis, and hepatosplenomegaly. Additional characteristic features in JMML include thrombocytopenia and elevated fetal hemoglobin. Myeloid progenitors in JMML display granulocyte-macrophage colony-stimulating factor (GM-CSF) hypersensitivity that has been attributed to dysregulated RAS/MAPK signaling. The latter is believed to result from mutually exclusive mutations involving *RAS*, *PTPN11*, and *NF1*. A third of patients with JMML that is not associated with Noonan's syndrome carry *PTPN11* mutations, whereas the incidence of *NF1* in patients without neurofibromatosis type 1 and *RAS* mutations is approximately 15% each. Drug therapy is relatively ineffective in JMML, and the treatment of choice is ASCT, which results in a 5-year survival of approximately 50%.

MDS/MPN-U

The WHO classifies patients with morphologic and laboratory features that resemble both MDS and MPN as *MDS/MPN overlap*. This category includes CMML, aCML, and JMML, which have been described above. In addition, MDS/MPN includes a fourth category referred to as *MDS/MPN, unclassifiable* (MDS/MPN-U). Diagnosis of MDS/MPN-U requires the presence of both MDS and MPN features that are not adequate to classify patients as CMML, aCML, or JMML. MDS/MPN includes the provisional category of RARS-T.

RARS-T is classified in the MDS/MPN category because it shares dysplastic features with RARS and myeloproliferative features with essential thrombocythemia (ET). In one study, 111 patients with RARS-T were compared with 33 patients with RARS. The frequency of *SF3B1* mutations in RARS-T (87%) was similar to that in RARS (85%). *JAK2 V617F* mutation was detected in 49% of RARS-T patients (including 48% of those mutated for *SF3B1*) but none of those with RARS. In RARS-T, *SF3B1* mutations were more frequent in females (95%) than in males (77%), and mean ring sideroblast counts were higher in *SF3B1*-mutated patients. Median overall survival was 6.9 years in *SF3B1*-mutated patients versus 3.3 years in unmutated patients. Six-year survival was 67% in *JAK2*-mutated patients versus 32% in unmutated patients. Multivariable analysis identified younger age and *JAK2* and *SF3B1* mutations as favorable factors.

In one series, 85 patients with non-RARS-T MDS/MPN, median age was 70 years, and 72% were males. Splenomegaly at presentation was present in 33%, thrombocytosis in 13%, leukocytosis in 18%, *JAK2* mutations in 30%, and abnormal karyotype in 51%; the most frequent cytogenetic abnormality was trisomy 8. Median survival was 12.4 months and favorably affected by thrombocytosis. Treatment with hypomethylating agents, immunomodulators, or ASCT did not appear to favorably affect survival.

MYELOPROLIFERATIVE NEOPLASM, UNCLASSIFIABLE (MPN-U)

The category of MPN-U includes MPN-like neoplasms that cannot be clearly classified as one of the other seven subcategories of MPN (Table 135e-4). Examples include patients presenting with unusual thrombosis or unexplained organomegaly with normal blood counts but found to carry MPN-characteristic mutations such as *JAK2* and *CALR* or display bone marrow morphology that is consistent with MPN. It is possible that some cases of MPN-U represent earlier disease stages in polycythemia vera (PV) or ET that fail to meet the threshold hemoglobin levels (18.5 g/dL in men or 16.5 g/dL in women) or platelet counts (450 × 10^9/L) that are required by the WHO diagnostic criteria. Specific treatment interventions might not be necessary in asymptomatic patients