Chronic Myelomonocytic Leukemia: Focus on Clinical Practice

Mrinal M. Patnaik, MD, and Ayalew Tefferi, MD

From the Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN.

CME Activity

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Abstract

Chronic myelomonocytic leukemia (CMML) is a clonal stem cell disorder with features that overlap those of myelodysplastic syndromes (MDSs) and myeloproliferative neoplasms (MPNs). Chronic myelomonocytic leukemia often results in peripheral blood monocytosis and has an inherent tendency to transform to acute myeloid leukemia. Clonal cytogenetic changes are seen in approximately 30% of patients, and molecular abnormalities are seen in more than 90%. Gene mutations involving *TET2* (~60%), *SRSF2* (~50%), *ASXL1* (~40%), and *RAS* (~30%) are frequent, with nonsense and frameshift *ASXL1* mutations being the only mutations identified thus far to have an independent negative prognostic effect on overall survival. Contemporary molecularly integrated prognostic models (inclusive of *ASXL1* mutations) include the Molecular Mayo Model and the Groupe Français des Myélodysplasies model. Given the lack of formal treatment and response criteria, management of CMML is often extrapolated from MDS and MPN, with allogeneic stem cell transplant being the only curative option. Hydroxyurea and other cytoreductive agents have been used to control MPN-like features, while epigenetic modifiers such as hypomethylating agents have been used for MDS-like features. Given the relatively poor response to these agents and the inherent risks associated with hematopoietic stem cell transplant, newer drugs exploiting molecular and epigenetic abnormalities in CMML are being developed. The creation of CMML-specific response criteria is a much needed step in order to improve clinical outcomes.

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Chronic myelomonocytic leukemia (CMML) is a clonal bone marrow (BM) disorder with features that overlap those of myelodysplastic syndromes (MDSs) and myeloproliferative neoplasms (MPNs) and has an inherent tendency to transform to acute myeloid leukemia (AML).[1,2] Chronic myelomonocytic leukemia often results in persistent (>3 months) peripheral blood (PB) monocytosis (absolute monocyte count [AMC], $>1 \times 10^9$/L).[1] In the 2008 World Health Organization (WHO) classification of hematologic malignancies, CMML is categorized as an MDS/MPN overlap syndrome, with other disorders in this group being juvenile myelomonocytic leukemia, atypical chronic myeloid leukemia, MDS/MPN-unclassifiable, and refractory anemia with ringed sideroblasts (RS) and thrombocytosis (currently a provisional entity) (Table).[2]

The median age at diagnosis of CMML is approximately 71 to 74 years, and the disorder has a male preponderance (1.5-3.0:1).[3-5] The exact incidence is unknown but is approximated at 4 cases per 100,000 persons per year.[6,7] Therapy-related CMML cases have been described, and like their MDS counterparts, are associated with poor clinical outcomes.[8,9] The presentation is variable, and the clinical heterogeneity was effectively captured by the French-American-British group's classification that categorized CMML into MDS-CMML and MPN-CMML on the basis of the latter having a white blood cell (WBC) count greater than 13×10^9/L.[10] Patients with an MDS phenotype tend to present with PB cytopenias, effort intolerance, easy bruising, recurrent infections, and transfusion dependance.[1] Those with an MPN phenotype tend to present with leukocytosis, monocytosis, hepatomegaly, splenomegaly, and features of myeloproliferation such as fatigue, night sweats, symptoms from organomegaly, bone pain, weight loss, and cachexia.[1] Rarely, CMML can present with leukemia cutis as an initial manifestation[11] or present directly with blast phase disease.[12]

DIFFERENTIAL DIAGNOSIS AND APPROACH TO PB MONOCYTOSIS

Peripheral blood monocytosis can be reactive or clonal. Reactive monocytosis is common and is often seen in association with viral infections and chronic infections/inflammatory conditions such as tuberculosis, brucellosis, leishmaniasis, subacute bacterial endocarditis, sarcoidosis, and connective tissue disorders.[1] Clues for viral infection—driven monocytosis include a temporal relationship with a febrile prodrome, the absence of immature myeloid cells (IMCs) on the blood smear (myelocytes, promyelocytes, and blasts), and an associated reactive lymphocytosis (including Downey cells).[1] Monocytosis is also an early sign of BM recovery following myelosuppression due to infections and medications, including chemotherapy. Clonal monocytosis is often persistent and is associated with hematopoietic stem cell disorders such as CMML, juvenile myelomonocytic leukemia, primary myelofibrosis (PMF), and AML with monocytic differentiation. In PMF, leukocytosis and monocytosis (monocytes, $>1 \times 10^9$/L) have been found to be independent factors adversely impacting overall survival (OS).[13] Figure 1 presents a diagnostic algorithm for PB monocytosis.

CMML DIAGNOSIS AND DIAGNOSTIC PITFALLS

The 2008 WHO criteria define CMML as a disorder characterized by (1) persistent PB monocytosis (monocytes, $>1 \times 10^9$/L), (2) absence of the Philadelphia chromosome and the *BCR-ABL1* (for expansion of gene symbols, see www.genenames.org) fusion oncogene, (3) absence of the *PDGFRA* or *PDGFRB* gene rearrangements, (4) less than 20% blasts and promonocytes in the PB and BM, and (5) dysplasia involving one or more myeloid lineages.[2] If myelodysplasia is absent or minimal, the diagnosis of CMML can still be made if the other requirements are met and an acquired clonal or molecular genetic abnormality is present in the hematopoietic cells or if the monocytosis has persisted for at least 3 months and other causes of monocytosis have been excluded.[1,2] Chronic myelomonocytic leukemia is further subclassified into CMML-1 (<5% circulating blasts and <10% BM blasts) and CMML-2 (5%-19% circulating blasts, 10%-19% BM blasts, or the presence of Auer rods irrespective of the blast count).[14-16] The median OS for CMML-1 and CMML-2 is approximately 38 and 24 months, respectively.[15,17]

The *BCR-ABL1* fusion oncogene defines chronic myeloid leukemia, a myeloid neoplasm in which monocytosis is uncommon.[18] The

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