doi.org/10.58931/cht.2025.4275

About the Author

Jacqueline Costello, MD

Dr. Jacqueline Costello is a general hematologist and assistant professor at Memorial University in St John's, NL. She is the clinical chair of the hematology research unit for Newfoundland and Labrador with focus in patient reported outcomes and overseeing clinical trials. She is in the home stretch in completing her masters of clinical epidemiology at Memorial University and has a passion for supervising learners' scholarly activity.

Affiliations: Memorial University, St John's, NL

Concise Review of Chronic Myelomonocytic Leukemia in Canada in 2025

Jacqueline Costello, MD

Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal myelodysplastic syndrome/myeloproliferative overlap neoplasm characterized by prominent monocytosis, with a very heterogeneous clinical presentation and an inherent risk of transforming to acute myeloid leukemia (AML). It is relatively rare, and the incidence is poorly defined. A Canadian analysis of a period of 20 years identified 1,440 cases and reported an incidence of 2.45 cases per 1,000,000.[1] Given that it often presents at an advanced age, with a median age of 70–76 years, aggressive therapeutic approaches are limited.

Diagnosis and Differential Diagnosis

CMML is diagnosed and classified according to either the International Consensus Classification (ICC) or the World Health Organization 5th edition (WHO5). The WHO5 CMML diagnostic criteria underwent major revisions, including lowering of the cut-off for absolute monocytosis, adopting of two new subtypes, and eliminating of CMML-0. The ICC diagnostic criteria also eliminated the CMML-0 category.

Monocytosis is characterized as a 3-month peripheral blood monocytosis with a notable decrease from previous to ≥0.5×10^9/L or relative monocytosis of ≥10% of leukocyte counts, consistent bone marrow morphology, <20% bone marrow or peripheral blasts and cytogenetic or molecular evidence of clonality.[2]

Two new disease subtypes with prominent clinical and genetic features were included based on white blood cell (WBC) count, myelodysplastic CMML (MD-CMML) with a WBC count of <13 × 10^9 and myeloproliferative CMML (MP-CMML) with a WBC count of >13×10^9 cells.[2] Two further categories of a) CMML-1 (<5% peripheral blood (PB) blasts, including promonocytes and <10% bone marrow (BM) blasts) and (b) CMML-2 (5%–19% PB blasts, including promonocytes and 10%–19% BM blasts and/or the presence of any Auer rods) remain. Additionally, therapy-related CMML (t-CMML) cases have been described (10% of all CMML cases), and, like their myelodysplastic syndromes (MDS) counterparts, have poorer overall survival and response to systemic therapies.

Variable	ICC	5th edition of the WHO Classification
Absolute monocyte count	• AMC ≥ 0.5 × 10^9/L, with monocytes being ≥10% of the WBC differential	• [b]AMC 20.5 × 10^9/L, with monocytes being >10% of the WBC differential
Cytopenias	• MDS-defining cytopenias	• Not specified
Clonality	• Abnormal karyotype, or myeloid driver mutations with a variant allele fraction >10% • Without a clonal marker the AMC ≥ 1.0 × 10^9/L, along with 25% BM blasts, or BM dysplasia, or an abnormal immunophenotype	• [c]Abnormal karyotype and/or presence of a myeloid driver mutation
CMML categorization	• [a]CMML-1: <5% PB blasts and <10% BM blasts • CMML-2: 5%-19% PB blasts and 10%-19% BM blasts, or the presence of Auer rods • WBC < 13 × 10^9/L-MD-CMML • WBC > 13 × 10^9/L-MP-CMML	• [a]CMML-1: <5% PB blasts and <10% BM blasts • CMML-2: 5%–19% PB blasts and 10%–19% BM blasts, or the presence of Auer rods • WBC <13 × 10^9/L-MD-CMML • WBC >13 × 10^9/L-MP-CMML
Bone marrow aspirate and biopsy	• Hypercellular marrows with increased BM monocytosis. No features of AML or MPN • <20% blasts	• [c]Dysplasia present in ≥1 cell lineage • [b]<20% blasts
Monocyte repartition-based flow cytometry	• Not included	• [c]Presence of classical monocytes (M01) >94%
Exclusionary criteria	• *BCR-ABL1* • Myeloid/lymphoid neoplasms with tyrosine kinase fusions	• [b]*BCR-ABL1* • MPN • Myeloid/lymphoid neoplasms with tyrosine kinase fusions

Table 1. International Consensus Classification and the 5th edition of the World Health Organization Classification systems for diagnosis of chronic myelomonocytic leukemia (CMML); *adapted from Khoury JD, et al., 2022*.

[a]In CMML promonocytes are considered blast equivalents and should be included in the blast count.
[b]Prerequisite criteria by the WHO for a diagnosis of CMML
[c]Supportive criteria for diagnosis of CMML. If the AMC ≥ 1 × 10^9/L, all prerequisite criteria and one supportive criterion should be present. If AMC > 0.5 × 10^9/L, then all prerequisite criteria and the presence of a clonal marker and BM dysplasia should be present. For the ICC cases without evidence of clonality, AMC 1.0 × 10^9/L and >10% of the WBC, and increased blasts (including promonocytes), or morphologic dysplasia, or an abnormal immunophenotype consistent with CMML would be required for the diagnosis of CMML. For cases lacking bone marrow findings of CMML, a diagnosis of CMUS (clonal monocytosis of undetermined significance) could be considered. If cytopenia is present, a diagnosis of CCMUS (clonal cytopenias with monocytosis of undetermined significance) could be entertained. In these diagnostic settings, however, an alternative cause for the observed monocytosis would have to be excluded based on appropriate clinicopathologic correlations. Myeloid and lymphoid neoplasms with tyrosine kinase fusions include recurrent abnormalities involving the following genes and rearrangements; *PDGFRA, PDGFRB, FGFR1, JAK2, FLT3, and ETV6-ABL1*.

Abbreviations: AMC: absolute monocyte count; **AML:** acute myeloid leukemia; **BM:** bone marrow; **ICC:** International Consensus Classification; **MDS:** myelodysplastic syndrome; **MPN:** myeloproliferative neoplasm; **WBC:** white blood cell count; **WHO**: World Health Organization.

Distinguishing CMML from other causes of monocytosis can be challenging, but certain findings can help support or exclude the diagnosis, including the flow cytometry immunophenotype (increased CD14+CD16- monocytes); exclusive genetic abnormalities, including *BCR::ABL1, PDGFRA-/B-, FGFR1*-rearrangement, and PCM1::JAK2; and patient having a prior myeloproliferative neoplasm (MPN). Dysplasia is generally more subtle and typically seen in <10% of mononuclear cells. CMML also often manifests more proliferative features, such as splenomegaly, leukocytosis, and constitutional symptoms.

BCR-ABL1-positive chronic myelogenous leukemia (CML) can present with monocytosis, especially in the presence of the p190 BCR-ABL1 fusion transcript, and should be excluded. The presence of *FLT3-ITD* or *NPM1* mutations may suggest the alternative diagnosis of AML, which masquerades initially as CMML.[3] In addition, the possibility of clonal hematopoiesis of indeterminate potential (CHIP) should be considered for cases with single gene mutations and a low variant allele frequency (VAF), particularly when mutations involve *DNMT3A, TET2*, or *ASXL1*.[2]

Molecular Pathogenesis

CMML often arises in the background of clonal hematopoiesis, with subsequent acquired mutations. Cytogenetic abnormalities are found in 30% of patients, of which trisomy 8 and various abnormalities of chromosome 7 are the most prevalent.[4] Approximately 90% of patients will have characteristic somatic mutations involving epigenetic regulation (*EZH2, ASXL1*, and *UTX TET2, DNMT3A, IDH1*, and *IDH2*), the spliceosome (*SF3B1, SRSF2, U2AF1, ZRSR2, PRPF8*), and signal transduction genes (*JAK2, KRAS, NRAS, CBL, PTPN11, NF1*, and *FLT3*).[5] Of these, mutations involving *TET2* (60%), *SRSF2* (50%), *ASXL1* (40%), and the oncogenic RAS pathway (30%) are the most frequent. In particular, the combination of *TET2* and *SRSF2* mutations is frequently observed in CMML, and has been shown to be highly specific for myeloid neoplasm with monocytosis.[6] VAF, nucleic acid, and amino acid changes of all likely pathogenic variants are important, as these can affect the prognostic relevance; missense mutations in ASXL1 do not seem to carry the same prognostic relevance as nonsense and frameshift mutations.

Risk Stratification

Several risk models developed for MDS to identify high-risk patients have also been used to risk stratify CMML, such as the International Prognostic Scoring System (IPSS) and its derivatives. Consensus for one widely used system has not been established, which is likely due to the relatively small number of patients and the heterogeneity between patients with CMML. However, three more recent models have taken more specific CMML features into account. The CMML-specific prognostic scoring system (CPSS-Mol) stratifies patients with CMML into four risk categories: low (0 risk factors), intermediate-1 (1 risk factor), intermediate-2 (2–3 risk factors), and high (≥4 risk factors) risk, with median OS of not reached, 64, 37, and 18 months, and 4-year leukemic transformation rates of 0%, 3%, 21%, and 48%, respectively.[7]

The Mayo Molecular Model (MMM) includes *ASXL1* mutations, absolute monocytes (AMC) $>10 \times 10^9$/L, hemoglobin (Hb) <10 g/dL, platelets $<100 \times 10^9$/L, and circulating immature myeloid cells (IMC), which were independently predictive of shorter OS. In this prognostic model, high (≥3 risk factors), intermediate-2 (2 risk factors), intermediate-1 (one risk factor), and low (no risk factors) risk categories have median OS of 16, 31, 59, and 97 months, respectively.[3] In a recent update of the model, the revised Mayo Molecular Model (MMMv2), *DNMT3A* is recognized as the most unfavourable and *PHF6* as the most favourable mutation, and this update also includes the important indicators of red blood cell transfusion need and leukocytosis ($\geq 13 \times 10^9$/L).

The Groupe Français des Myélodysplasies (GFM) risk model demonstrated an adverse prognostic effect for *ASXL1*, age >65 years, WBC $>15 \times 10^9$/L, platelet count $<100 \times 10^9$/L, and Hb <10 g/dL in females and <11 g/dL in males. The GFM model assigns three adverse points for WBC $>15 \times 10^9$/L and two adverse points for each one of the other risk factors, resulting in a three-tiered risk stratification: low (0–4 points), intermediate (5–7), and high (8–12), with respective median OS of 56, 27.4, and 9.2 months.[8]

Risk-Adapted Therapy

Pretreatment evaluation of a patient with CMML to identify disease-associated symptoms and evaluate their medical fitness is crucial for goals of care discussions regarding whether systemic therapies are recommended. Many patients with CMML who do not have significant

cytopenia or symptomatology may be observed without treatment. No clear thresholds exist for the initiation of therapy, but like for MDS, Hb levels <100 g/L and platelets <30×10^9/L often trigger therapy. There is no demonstrated WBC threshold to start treatment in the case of myeloproliferation. Therapy is also often incited in the case of symptomatic splenomegaly, extramedullary disease, or constitutional symptoms.

Treatment options for CMML have evolved over the last three decades from using toxic chemotherapy to DNA methyltransferase inhibitors (DNMTi)/ hypomethylating agents (HMA). The approval of these drugs in Canada was based on the inclusion of patients with CMML in MDS-predominant trials.[4,13] When selecting therapy for patients with CMML considered "unfit", it is important to select a therapy that targets the nature of the symptoms (i.e., cytopenic patients may have a better response with HMAs), and myeloproliferative patients may benefit from cytoreduction (hydroxyurea).

HMAs

HMAs remain the only approved novel drugs for the management of CMML in Canada and are associated with overall response rates (ORR) of 40%–50% and true complete remission (CR) rates of <20%.[9] No randomized trial has directly compared azacitidine versus decitabine for CMML. Predictors of response to HMA have not been established, but there are some suggestions that the *ASXL1*^{WT}/*TET2*^{MT} genotype might be the most predictive.[10] Several studies indicate that MP-CMML still has a shorter survival than MD-CMML when treated with HMAs.[9,11] However, there is no obvious trend correlating response to HMAs in CMML with the extent of myeloproliferation.[9]

5-Azacitidine

The pivotal North American CALGB 9221 study (n = 191) only included 14 patients with CMML, and the European AZA-001 study only included 11 patients with CMML (all MD-CMML).[12,13] The ORR for these studies was approximately 40%, but complete and sustained responses were found in fewer than 20% of patients.

Cedazuridine/Decitabine

The efficacy of single-agent intravenous decitabine has been assessed in a handful of trials with few patients, and ORRs were detected to be between 25–40%.[14] Also in trials investigating the combination oral therapy cedazuridine and a cytidine deaminase (CDA) inhibitor, the MDS-focused Phase 3 Ascertain and the Phase 2 ASTX727 study[15], very few patients with CMML patients were included. In these studies, patients with CMML were found to have CR rates of <20% and a mean duration of response of about 9 months. However, close to 50% of patients achieved platelet and/or red blood cell independence for the duration of response.

Cytoreductive Therapy

Hydroxyurea (Hydrea)

Hydroxyurea has been used to offset splenomegaly and other constitutional symptoms of CMML with the goal of achieving a balance between reducing symptoms and exacerbating neutropenia, anemia, and thrombocytopenia. It is not clear whether CMML-MP responds better to HMAs or hydroxyurea. The Phase 3 DACOTA study showed that compared with hydroxyurea, front-line treatment with decitabine did not improve event-free survival in patients with advanced myeloproliferative CMML. However, decitabine was associated with a lower risk of CMML progression or transformation to acute leukemia in this study, but the trade-off with this therapy are the Grade ≥3 infections in 33% of patients treated with decitabine, which is lower at 18% in those treated with hydroxyurea, and hospitalization occurred in 60% and 40%, respectively.[6] Other agents, such as etoposide and cytarabine, have been used, but have not been shown to be more effective than hydroxyurea.[8]

Allogeneic Stem Cell Transplant

Allogeneic stem cell transplantation (alloSCT) remains the only curative therapy but is only an option for a fraction of patients due to advanced median age and co-morbidities excluding them. OS for patients with CMML ranges from 30–40% at 5 years after alloSCT, owing to relapses and non-relapse-related mortality, such as graft vs. host disease (GvHD) and infection.[16] Pre-transplantation treatment should be designed to maximize bone marrow responses while minimizing toxicity, and should be selected using the characteristics of the disease as well as the comorbidities of the patient.

A report on the outcomes of alloSCT after azacitidine-based low-intensity treatment in 277 high-risk patients with MDS and CMML, showed similar outcomes to historical controls

who received transplantation after intensive chemotherapy. This has led to the wide use of HMAs pre-transplant for lower blast burden.[11] HMA may also be considered in patients with mutated *TET2* and wild-type *ASXL1* as they appear to have higher response rates to HMAs, including in CMML.[6]

Response to Therapy

The MDS/MPN international working group (IWG) formulated specific disease response criteria to include CMML. Response to therapy can be judged based on clinical benefit, hematologic response, resolution of hepatosplenomegaly/extramedullary disease, morphologic response in bone marrow, and improvement of quality of life.[17]

Relapsed Disease

Unfortunately, based on clinical experience, for relapsing patients with progressive disease who have previously been exposed to HMA or received an alloSCT, prognosis is poor, with survival measured in weeks to months. Patients with CMML at this stage are strongly encouraged to enter clinical trials.

Supportive Care

Erythropoietin-stimulating agents, prophylactic antibiotics, and other supportive care have not been widely studied in CMML, but it has been demonstrated to benefit some MDS populations.[18]

Conclusion And Future Directions

CMML is a rare MDS/MPN crossover neoplasm with heterogeneous clinical outcomes, and the disease is often underrepresented in trials. However, over the last decade, epigenetics and pathogenesis of the disease have gained traction in separating it from MDS, which has resulted in trials with more specific novel therapies. Novel targets, including RAS, BCL2, JAK-STAT, and SRSF2, as well as bispecific T-cell engagers, have been explored with limited to modest success in small numbers of patients in early phase trials.[19,20] A PLK1 inhibitor, onvansertib, is currently being tested in hydroxyurea and/or HMA-relapsed, refractory, or intolerant patients (NCT05549661). Similarly, given that high-dose intravenous ascorbic acid can enhance unmutated *TET2* and *TET3* catalytic activity, there is a pilot study ongoing assessing high-dose intravenous ascorbic acid with decitabine in newly diagnosed CMML (NCT03418038). Additionally, EP31670 is a novel oral dual BRD4/p300 inhibitor that is being tested in *ASXL1* mutant relapsed/refractory CMML (NCT05488548). Given the high frequency of spliceosome mutations in CMML (*SRSF2*), several spliceosome inhibitors are also being explored. For these patients, excellent goals of care discussions are essential, and it is recommended to continue encouraging enrollment in clinical trials.

Correspondence

Jacqueline Costello, MD
Email: jacqueline.costello@easternhealth.ca

Financial Disclosures

J.C.: None declared.

References

1. Le M, Ghazawi F, Popradi G, Glassman S, Sasseville D, Litvinov I. Epidemiology and geographic trends for chronic myelomonocytic leukemia in Canada. J Am Acad Dermatol. 2018;79(AB130):1.
2. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022;36(7):1703-19.
3. Savona MR, Malcovati L, Komrokji R, Tiu RV, Mughal TI, Orazi A, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. Blood. 2015;125(12):1857-65.
4. Patnaik MM, Tefferi A. Chronic myelomonocytic leukemia: 2024 update on diagnosis, risk stratification and management. Am J Hematol. 2024;99(6):1142-65.
5. Patnaik MM, Itzykson R, Lasho TL, Kosmider O, Finke CM, Hanson CA, et al. ASXL1 and SETBP1 mutations and their prognostic contribution in chronic myelomonocytic leukemia: a two-center study of 466 patients. Leukemia. 2014;28(11):2206-12.
6. Patnaik MM, Wassie EA, Padron E, Onida F, Itzykson R, Lasho TL, et al. Chronic myelomonocytic leukemia in younger patients: molecular and cytogenetic predictors of survival and treatment outcome. Blood Cancer J. 2015;5(1):e270.
7. Such E, Germing U, Malcovati L, Cervera J, Kuendgen A, Della Porta MG, et al. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. Blood.
8. Wattel E, Guerci A, Hecquet B, Economopoulos T, Copplestone A, Mahe B, et al. A randomized trial of hydroxyurea versus VP16 in adult chronic myelomonocytic leukemia. Groupe Francais des Myelodysplasies and European CMML Group. Blood. 1996;88(7):2480-7.
9. Coltro G, Mangaonkar AA, Lasho TL, Finke CM, Pophali P, Carr R, et al. Clinical, molecular, and prognostic correlates of number, type, and functional localization of TET2 mutations in chronic myelomonocytic leukemia (CMML)-a study of 1084 patients. Leukemia. 2020;34(5):1407-21.
10. Itzykson R, Kosmider O, Renneville A, Gelsi-Boyer V, Meggendorfer M, Morabito M, et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. J Clin Oncol. 2013;31(19):2428-36.
11. Robin M, de Wreede LC, Padron E, Bakunina K, Fenaux P, Koster L, et al. Role of allogeneic transplantation in chronic myelomonocytic leukemia: an international collaborative analysis. Blood. 2022;140(12):1408-18.
12. Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol. 2002;20(10):2429-2440.
13. Fenaux P, Mufti GJ, Santini V, Finelli C, Giagounidis A, Schoch R, et al. Azacitidine (AZA) Treatment prolongs overall survival (OS) in higher-risk MDS patients compared with conventional care regimens (CCR): Results of the AZA-001 phase III study. Blood. 2007;110(11):817.
14. Wijermans PW, Ruter B, Baer MR, Slack JL, Saba HI, Lubbert M. Efficacy of decitabine in the treatment of patients with chronic myelomonocytic leukemia (CMML). Leuk Res. 2008;32(4):587-91.
15. Garcia-Manero G, Griffiths EA, Steensma DP, Roboz GJ, Wells R, McCloskey J, et al. Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study. Blood. 2020;136(6):674-683.
16. Ocheni S, Kröger N, Zabelina T, Zander AR, Bacher U. Outcome of allo-SCT for chronic myelomonocytic leukemia. Bone Marrow Transplant. 2009;43(8):659-61.
17. Itzykson R, Santini V, Thepot S, Ades L, Chaffaut C, Giagounidis A, et al. Decitabine Versus Hydroxyurea for Advanced Proliferative Chronic Myelomonocytic Leukemia: Results of a Randomized Phase III Trial Within the EMSCO Network. J Clin Oncol. 2023;41(10):1888-97.
18. Xicoy B, Germing U, Jimenez MJ, Garcia O, Garcia R, Schemenau J, et al. Response to erythropoietic-stimulating agents in patients with chronic myelomonocytic leukemia. Eur J Haematol. 2016;97(1):33-8.
19. Hiwase D, Ross DM, Lane SW, Thompson-Peach C, Fong CY, Yong ASM, et al. Lenzilumab in Addition to Azacitidine Improves Complete Response Rates in Chronic Myelomonocytic Leukemia. Blood. 2023;142:1847.
20. Croden J, Chien K, Borthakur G, DiNardo C, Hammond D, Short N, et al. A phase I open label study of fostamatinib, a SYK inhibitor, in patients with lower-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. EHA Library. 2025;4160712:PS1637.