How I diagnose and treat chronic myelomonocytic leukemia

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Abstract
Chronic myelomonocytic leukemia (CMML) is a myelodysplastic syndrome/myeloproliferative overlap neoplasm characterized by sustained peripheral blood monocytosis and an inherent risk for transformation to acute myeloid leukemia (15-30% over 3-5 years). While CMML is morphologically classified into CMML-0, 1 and 2 based on peripheral blood and bone marrow promonocyte/blast counts, a more clinically relevant classification into dysplastic and proliferative subtypes, based on the presenting white blood cell count, is helpful in prognostication and therapeutics. CMML is a neoplasm associated with aging, occurring on the background of clonal hematopoiesis, with TET2 and SRSF2 mutations being early initiating events. The subsequent acquisitions of ASXL1, RUNX1, SF3B1 and DNMT3A mutations usually give rise to dysplastic CMML, while ASXL1, JAK2V617F and RAS pathway mutations give rise to proliferative CMML. Patients with proliferative CMML have a more aggressive course with higher rates of transformation to acute myeloid leukemia. Allogeneic stem cell transplant remains the only potential cure for CMML; however, given the advanced median age at presentation (73 years) and comorbidities, it is an option for only a few affected patients (10%). While DNA methyltransferase inhibitors are approved for the management of CMML, the overall response rates are 40-50%, with true complete remission rates of <20%. These agents seem to be particularly ineffective in proliferative CMML subtypes with RAS mutations, while the TET2 mutant/ASXL1 wildtype genotype seems to be the best predictor for responses. These agents epigenetically restore hematopoiesis in responding patients without altering mutational allele burdens and progression remains inevitable. Rationally derived personalized/targeted therapies with disease-modifying capabilities are much needed.

Introduction
Chronic myelomonocytic leukemia (CMML) is a myeloid neoplasm characterized by sustained peripheral blood monocytosis (absolute monocyte count ≥1x10^9/L, with monocytes accounting for ≥10% of the white blood cells), predominantly arising in the context of age-related clonal hematopoiesis, with overlapping features of myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN). The exact incidence and prevalence rates for CMML are hard to define, with Surveillance, Epidemiology, and End Results (SEER) registry data demonstrating an incidence of 0.4 cases per 100,000, with most studies showing a clear male preponderance. The median age of presentation for CMML patients is between 70-75 years, with “young CMML” patients being operationally defined as those who present at <65 years of age. At the genome level CMML is relatively homogeneous, demonstrating approximately 10-12 somatic variants per kilobase of coding region, with most pathogenic variants involving TET2 (60%), ASXL1 (40%), SRSF2 (50%) and RAS pathway (30%) genes. However, clinically the disease is very heterogenous in presentation and outcomes, making diagnostic, prognostic and therapeutic decision-making challenging. Broadly, CMML can be classified into dysplastic CMML (dCMML), presenting with cytopenias and clinical signs and symptoms related to the same (fatigue, bruising and transfusion dependence) and proliferative CMML (pCMML), presenting with significant myeloproliferation, extramedullary hematopoiesis and associated constitutional symptoms (fever, weight loss, night sweats, anorexia, pruritus, bone pain and cachexia). From a classification perspective, for several years CMML was classified as a subtype of MDS, with the World Health Organization (WHO) rightfully and formally classifying CMML as an MDS/MPN overlap neoplasm, from 2002 on...
Figure 1. Clonal evolutionary dynamics in patients with chronic myelomonocytic leukemia. The dynamics of clonal evolution in patients with chronic myelomonocytic leukemia (CMML) demonstrating the early acquisition of TET2 and SRSF2 mutations in hematopoietic stem cells and common myeloid progenitor cells, followed by acquisition of signaling mutations (NRAS, CBL, KRAS and PTPN11), transcription factors (RUNX1) and pre mRNA splicing (SF3B1 and U2AF1), shaping clinical phenotypes (Figure 1). There are pCMML subtypes in which oncogenic RAS pathway mutations (NRAS, CBL, KRAS and PTPN11) are clear initiating driver mutations, occurring early in the course of disease, associated with poor outcomes (decreased survival and higher rates of transformation to acute myeloid leukemia [AML]) (Figure 1). Unlike in MDS, MPN or AML, TP53 mutations are extremely infrequent in CMML (<1%), and are only really encountered at the time of CMML to AML transformation, or in the context of therapy-related CMML. The 2016 iteration of the WHO classification of myeloid neoplasms has outlined diagnostic criteria for CMML which include the presence of sustained peripheral blood monocytosis, absence of reactive causes, the presence of <20% blasts and promonocytes (blast equivalents) in the peripheral blood and bone marrow, and exclusion of molecularly
defined myeloid neoplasms that can present with monocytosis (BCR-ABL1, PDGFA, PDGFRB, FGFR1 and PCM1-JAK2 rearrangements), with or without dysplasia (Table 1). In the absence of dysplasia, a diagnosis of CMML can be made if the monocytosis has persisted for ≥3 months, reactive causes have been excluded, or somatic cytogenetic or molecular markers frequent in CMML (e.g., ASXL1, TET2, SRSF2 and SETBP1) can be documented. While this approach is very reasonable, there are limitations and important nuances associated with these criteria. While absolute monocytosis is uncommon in chronic myeloid leukemia, it can occur in BCR-ABL1 p190 isoform-driven disease and, regardless of the presence or absence of a “myelocyte bulge”, assessment for BCR-ABL1 fusions by fluorescence in situ hybridization, cytogenetics, and/or molecular techniques should be pursued. Chromosomal translocations/rearrangements involving PDGFA and PDGFRB can give rise to myeloid neoplasms, often characterized by prominent eosinophilia and responsiveness to imatinib. Among these, PDGFRB-rearranged myeloid neoplasms can be associated with absolute monocytosis (<1% of all cases morphologically diagnosed as CMML), usually with concomitant eosinophilia, and given their unique responsiveness to imatinib are best classified as molecularly defined neoplasms and not as CMML. More than 20 fusion partner genes have been described with PDGFRB, with t(5;12)(q31-q32;p13), giving rise to the ETV6(TEL)-PDGFRB fusion, being the most common. The FIP1L1-PDGFR fusion arising due to the CHIC2 deletion is the most common PDGFR fusion and is uncommonly associated with monocytosis. While most PDGFRB rearrangements can be identified by conventional karyotyping, the FIP1L1-PDGFR fusion is karyotypically occult and can only be detected by fluorescence in situ hybridization or molecular analyses. Similarly, FGFR1 and PCM1-JAK2 rearrangements are very uncommon causes of monocytosis and are more commonly associated with eosinophilia. Monocytosis can occur in the context of other myeloid neoplasms such as MDS and MPN and is associated with poor outcomes in MPN. Among classical MPN-driver mutations, while JAK2V617F can occur in 10% of CML patients, mutations involving MPL and CALR are extremely infrequent and their detection should raise questions with regards to a bona fide CML diagnosis. Occasionally NPM1 and FLT3 driver mutations are identified in CML patients with excess blasts (5-19%). For all practical purposes 1 consider these cases as acute myelomonocytic leukemia in evolution and treat them as such. Reactive monocytosis is very common in practice and while viral infections and recovering bone marrow (from injury, drugs or chemotherapy) are frequent causes, sustained reactive monocytosis is more common in chronic infections such as subacute bacterial endocarditis, tuberculosis, brucellosis, leishmaniasis and leprosy and in autoimmune/inflammatory disorders such as systemic lupus erythematosus, sarcoidosis and mixed connective tissue...
Role of flow cytometry, next-generation sequencing and bone marrow biopsies in the diagnosis of chronic myelomonocytic leukemia

Conventional flow cytometry has a limited diagnostic role in CMML, given that immature/neoplastic monocytes do not express unique surface markers and that promonocytes/monoblasts are frequently CD34-negative (blast marker). Flow abnormalities that can be detected in CMML include abnormal myeloid maturation patterns involving CD11b, CD13 and CD16, along with aberrant expression of CD56 on monocytes. Monocyte repartitioning by flow cytometry has gained popularity, especially given its ability to differentiate CMML from other reactive and clonal causes of monocytosis. Based on the expression of CD14 and CD16, monocytes can be divided into three categories: CD14+/CD16− classical (M01), CD14lo/CD16+ intermediate (M02), and CD14−/CD16− non-classical monocytes (M03) (Figure 2). These subsets differ in their chemokine receptor expression, phagocytic activity, epigenetic profiles and have unique metabolic pathway dependencies.

In CMML, a pivotal study demonstrated an increase in the M01 subset, with an established cutoff >94% being associated with sensitivity and specificity values of 90.6% and 95.1%, respectively. These findings have been validated independently and this method importantly is effective in identifying MDS patients whose disease eventually evolves into CMML and in distinguishing CMML from MPN with monocytosis. False negative findings secondary to autoimmunity/inflammation (expansion of the M02 fraction) and false positive findings in myeloid neoplasms such as MDS, atypical chronic myeloid leukemia and classical chronic myeloid leukemia have been documented. Reactive monocytosis can also be seen in the context of metastatic visceral neoplasms, either due to enhanced mobilization of monocytes from the bone marrow, or due to increased monopoiesis mediated by CCL2 (C-C motif chemokine ligand 2).

Next-generation sequencing assays are an important part of the diagnosis and prognostication of CMML. Virtually all CMML patients will have detectable somatic mutations involving genes regulating the epigenome, splicing, signaling and transcription. Clonal compositions help to define pCMML and dCMML subtypes and contribute towards AML transformation. Single-cell sequencing data have shown that TET2 mutations are usually the founder mutations occurring at the hematopoietic stem cell level. These mutations impact multipotent progenitor and common myeloid progenitor cells, skewing differentiation towards granulomonocytic progenitors and mature monocytes, respectively (Figure 1). Second-order mutations tend to accumulate in multipotent progenitor and common myeloid progenitor cells, often involving additional sites/alleles on TET2, spliceosome component genes (SF3B1 and RUNX1) and additional epigenetic regulators (ASXL1, rarely EZH2). Signaling mutations, such as NRAS, CBL, PTPN11, KRAS, NF1 and JAK2V617F, can sometimes be early/founder mutations, with inherent hypersensitivity of hematopoietic stem/progenitor cells to granulocyte-macrophage colony-stimulating factor (like the pCMML pediatric counterpart, juvenile myelomonocytic leukemia), but can also be later/subclonal events, giving rise to dCMML. Similarly, acquisition of additional epigenetic (DNMT3A, rarely IDH1/2) and splicing mutations (SF3B1) and mutations involving transcription factors (RUNX1) often gives rise to a dCMML phenotype. Somatic copy number alterations, especially copy neutral loss of heterozygosity, is common in CMML and frequently involves TET2 (4q24) and CBL (11q23), playing a role in clonal evolution. Genetic alterations involving protein coding regions, including copy number gains and losses in driver mutations were only able to explain 44% of CMML cases that transformed to AML, indicating that mechanisms of
AML transformation remain to be elucidated.\textsuperscript{10} It is important to note that germline variants have been implicated in the pathogenesis of CMML, with cases having been documented in the context of germline mutations involving \textit{RUNX1}, \textit{ANKRD26}, \textit{ETV6}, \textit{CHEK2}, \textit{CDK2NA} and \textit{GATA2}.\textsuperscript{46,47} Recently, a 700 kb germline duplication localized to 14.q32.2, resulting in overexpression of \textit{ATG2B} and \textit{GSKIP} genes, was described and has been associated with familial MPN and CMML.\textsuperscript{48} Based on family histories, age of onset and the heterozygous nature of variant allele fractions, I routinely assess germline DNA from extracted hair follicles/skin fibroblasts to assess for germline predisposition syndromes.\textsuperscript{49} In CMML, bone marrow biopsies are often hypercellular with granulocytic hyperplasia and mild to modest dysplasia (Figure 3D, E). Bone marrow monocytosis can be present, but is often difficult to appreciate and immunohistochemical studies that aid in the identification of monocytes and

\textbf{Figure 3. Peripheral blood and bone marrow findings in patients with chronic myelomonocytic leukemia.} (A) Peripheral blood smear with hypogranular neutrophil (black arrow) and promonocytes (black arrowhead). (B) Bone marrow aspirate with promonocytes (black arrowhead). (C) Butyrate esterase/chloroacetate esterase stain demonstrates numerous butyrate esterase-positive monocytes, as well as dual esterase-positive cells (inset). (D) Bone marrow aspirate with increased blasts. (E) Bone marrow biopsy demonstrating a hypercellular bone marrow. (F) Small plasmacytoid dendritic cell nodules CD123\textsuperscript{*} (left) and CD303\textsuperscript{*} (right).
their precursors are recommended (Figure 3C). Almost 80% of patients will demonstrate micro-megakaryocytes with abnormal nuclear contours and lobations, and 20–30% of patients can have an increase in reticulin fibrosis. Approximately 30% of patients demonstrate nodules composed of mature plasmacytoid dendritic cells that are clonal (CD123+, lineage-negative, CD45+, CD11c+, CD33+, HLA-DR+, BDCA-2+ and BDCA-4+), often have RAS pathway mutations and predict for an inferior AML-free survival (Figure 3F). The identification of promonocytes requires expertise and these cells should be summated with blasts when estimating the blast count (Figure 3A, B). Promonocytes are described as monocytic precursors that have a delicately convoluted, folded or grooved nucleus with finely dispersed chromatin, a small indistinct or absent nucleolus, and finely granulated cytoplasm. On immunophenotyping the abnormal bone marrow cells often express myelomonocytic antigens such as CD13 and CD33, with variable expression of CD14, CD68 and CD64. Markers of aberrant expression include CD2, CD15, and CD56 or decreased expression of CD13, CD14, HLA-DR, CD64 or CD36. The presence of myeloblasts can often be detected by expression of CD34. The most reliable markers on immunohistochemistry include CD68R and CD163. On cytochemical analysis, monocytes are often positive for non-specific esterases and lysozyme, while the granulocytic precursors are often positive for lysozyme and chloroacetate esterase (Figure 3C). This technique can help to differentiate CMML from other overlap neoplasms in which bone marrow monocytosis is uncommon. Conventional karyotyping on the bone marrow is important for cytogenetic risk stratification, with approximately 70–80% of patients demonstrating a normal karyotype. Common abnormalities include +8 and −Y, with isolated del5q, complex and monosomal karyotypes being very uncommon (complex and monosomal karyotypes can be seen in patients with therapy-related CMML). The CMML-specific prognostic scoring system (CPSS) and the Mayo-French cytogenetic risk stratification system are two commonly used karyotype-based prognostic models for patients with CMML (Table 2).

How I approach chronic myelomonocytic leukemia variants and molecularly defined entities with monocytosis

The diagnosis and management of CMML variants and molecularly defined entities presenting with monocytosis, mimicking CMML, require special attention. These variants can broadly be divided into three categories: (i) oligomonocytic CMML; (ii) CMML associated with a concomitant myeloid neoplasm; and (iii) molecularly defined entities with monocytosis. **Oligomonocytic CMML.** This category encompasses patients who present with sustained relative monocytosis (≥10% of white blood cells) and absolute monocytosis not meeting current diagnostic criteria for CMML (absolute monocyte count 0.5–<1.0x10⁹/L). Based on the 2016 WHO classification, these patients would be classified as having either MDS or MDS/MPN-Unclassifiable. Except for an absolute monocyte count of ≥1x10⁹/L, if these patients meet other CMML diagnostic criteria, along with a M01 fraction >94% on monocyte repartitioning flow cytometry, and a molecular signature consistent with CMML (TET2, SRSF2, and ASXL1), I consider them as having oligomonocytic CMML and follow and manage them as such. Over time, several of these patients will have clonal evolution to either CMML or secondary AML.

**CMML associated with a concomitant myeloid neoplasm.** This category includes several variants, with the two most important being systemic mastocytosis (SM) with CMML (SM-CMML) and JAK2V617F-mutant CMML. CMML is the most frequent hematologic neoplasm associated with SM. I diagnose SM-CMML in patients who meet WHO criteria for both entities. In these patients, the SM component can present as either indolent or aggressive SM, with mast cell leukemia being extremely infrequent. In a Mayo Clinic study of 50 patients with SM-CMML, survival outcomes were similar to those of patients with CMML (24 months for SM-CMML vs. 18 months for CMML; P=0.08), There was a higher frequency of KIT and CBL mutations in SM-CMML and CMML-based prognostic models were not effective in risk stratification in this condition due to the confounding impact of SM. In CMML patients who have a detectable KITD816V mutation, a known driver oncogene in SM (>90% of cases), I universally assess for concomitant SM clinically and by using laboratory techniques such as serum tryptase levels (>20 ng/mL), bone marrow morphology, flow cytometry (aberrant expression of CD2 and/or CD25 on mast cells) and immunohistochemistry (CD117 and tryptase). For SM-CMML patients there are several exciting KIT-directed targeted therapies for the SM component (e.g., midostaurin and avapritinib) and given that in SM-CMML, neoplastic monocytes are also often KIT mutated, these drugs can sometimes effectively decrease monocyte counts and infiltrative disease burden. JAK2V617F-mutant CMML usually gives rise to a pCMML subtype with higher hemoglobin levels and absolute monocyte counts, with monocyte repartitioning by flow being a useful tool to distinguish this entity from MPN with monocytosis. On rare occasions, it becomes very difficult to distinguish the concomitant presence of a JAK2V617F MPN with bona fide CMML and in these instances, I manage each symptomatic component individually.

**Molecularly defined entities with monocytosis.** This category includes myeloid and lymphoid neoplasms pres-
ent with monocytosis in the context of rearrange-
ments involving PDGFRA, PDGFRB, FGFR1 and PCM1-JAK2. 
These entities are best designated by their molecular 
drivers and are currently not referred to as CMML. The 
recognition of these entities is very important given that 
they can present with a lymphoproliferative component 
and eosinophilia and can be targeted with tyrosine kinase 
inhibitors.19,60

**Table 2.** Chronic myelomonocytic leukemia risk stratification models.

| Model | Risk categories | Survival | Risk factors |
|-------|-----------------|----------|--------------|
| CMML-Specific Cyogenetic Risk Stratification (CPSS) | Low risk | 35% 5-yr OS | • Normal or isolated loss of Y |
|       | Intermediate risk | 26% 5-yr OS | • All others |
|       | High risk | 4% 5-yr OS | • Trisomy 8, chromosome 7 abnormalities, or complex karyotype |
| Mayo-French Cyogenetic Risk Stratification System | Low risk | 41 mo MS | • Normal, sole -Y, and sole der(3q) |
|       | Intermediate risk | 21 mo MS | • All abnormalities not in low- or high-risk categories |
|       | High risk | 3 mo MS | • Complex and monosomal karyotypes |
| Mayo Molecular Model (MMM) | Low risk (0 points) | 97 mo MS | • AMC >10x10⁹/L (2 points) |
|       | Intermediate-1 risk (1.5 - > 2.5 points) | 59 mo MS | • Presence of circulating IMC (2 points) |
|       | Intermediate-2 risk (2.5-4.5 points) | 31 mo MS | • Hemoglobin level <10 g/dL (2 points) |
|       | High risk (≥ 5 points) | 16 mo MS | • ASXL1 mutation (1.5 points) |
| Groupe Francophone de Myelodysplasies (GFM) | Low risk (0-4 points) | 65 mo MS | • Platelet count <100x10⁹/L (1.5 points) |
|       | Intermediate risk (5-7 points) | 28 mo MS | • WBC >15x10⁹/L (3 points) |
|       | High risk (8-12 points) | 17 mo MS | • ASXL1 mutations (2 points) |
| CMML-Specific Prognostic Scoring System (CPSS-Mol) | Points for mutation status | Points for karyotype status based on CPSS | Genetic risk* for CPSS Mol model |
|       | WT | MT | Normal or −Y | All other abnormalities | Trisomy 8, Monosomal, Complex | Low | Int-1 | Int-2 | High |
|       | ASXL1 | 0 | 1 | 0 | 1 | 2 | P |
|       | NRAS | 0 | 1 | 0 | 1 | 1 | 1 |
|       | RUNX1 | 0 | 2 | 0 | 1 | 2 | 2 |
|       | SETBP1 | 0 | 1 | 0 | 1 | 3 | ≥3 |

OS: overall survival; yr: year; mo: months; MS: median survival; AMC: absolute monocyte count; IMC: immature myeloid cells; WBC: white blood cell count; WHO: World Health Organization; FAB: French American and British classification; WT: wild type, MT: mutant, AML-TR: acute myeloid leukemia transformation rate, RBC transf: red blood cell transfusion; CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm.
How I prognosticate outcomes for patients with chronic myelomonocytic leukemia

While there are numerous prognostic models for patients with CMML, models such as the Bournemouth, Lille, International Prognostic Scoring System (IPSS) and revised-IPSS scores are primarily designed for patients with MDS and excluded patients with pCMML.61,62 The MD Anderson prognostic system (MDAPS) is CMML-specific and identified a hemoglobin level <12 g/dL, presence of circulating immature myeloid cells (myelocytes, promyelocytes and metamyelocytes), absolute lymphocyte count >2.5x10^9/L and ≥10% bone marrow blasts as independent predictors for inferior survival.63 The Global MDAPS was then developed for patients with MDS, secondary MDS and CMML, with prognostic factors including; older age, poor performance status, thrombocytopenia, anemia, increased bone marrow blasts, leukocytosis (>20x10^9/L), chromosome 7 or complex cytogenetic abnormalities and a prior history of red blood cell transfusions.64 This model identified four prognostic groups with median survivals of 54 (low), 25 (intermediate-1), 14 (intermediate-2) and 6 months (high), respectively.64 The CPSS model was developed in Europe and identified pCMML versus dCMML subtypes, WHO CMML-subtypes, red blood cell transfusion dependency and the CPSS cytogenetic risk stratification system as being prognostic for survival.54,65 The Mayo prognostic model identified hemoglobin <10 g/dL, platelet count <100x10^9/L, absolute monocyte count >10x10^9/L and circulating immature myeloid cells as being independently prognostic.6 The discovery of somatic mutations in CMML resulted in the development of contemporary molecular prognostic models. The Group Francophone des Myelodysplasies (GFM) demonstrated an adverse prognostic effect for truncating ASXL1 mutations in 312 patients with CMML; additional risk factors included age >65 years, white blood cell count >15x10^9/L, platelet count <100x10^9/L and hemoglobin <10 g/dL in females and <11 g/dL in males.5 The GFM model assigns three adverse points for white blood cell count >15x10^9/L and two adverse points for each one of the remaining risk factors, resulting in a three-tiered risk stratification; low (0–4 points), intermediate (5–7) and high (8–12), with respective median survivals of 56, 27.4 and 9.2 months.5 To further clarify the prognostic relevance of ASXL1 mutations, the Mayo Molecular Model (MMM) was developed as a collaborative effort between the GFM and Mayo Clinic (n=466).66 Adverse prognostic factors included truncating ASXL1 mutations, absolute monocyte count >10x10^9/L, hemoglobin <10 g/dL, platelets <100x10^9/L and circulating immature myeloid cells. Based on these variables a regression coefficient-based prognostic model was developed with the following risk categories; high (≥3 risk factors), intermediate-2 (2 risk factors), intermediate-1 (1 risk factor), and low (no risk factors) risk, with median survivals of 16, 31, 59 and 97 months, respectively.67 The CPSS model was also updated to include gene mutations involving ASXL1, RUNX1, NRAS and SETBP1 (CPSS-Mol).6 Gene mutations along with karyotypic abnormalities are used to calculate the CPSS genetic score. One point each is assigned for an intermediate-1 genetic score, white cell count ≥13x10^9/L, bone marrow blasts ≥5% and red blood cell transfusion dependency, two points for intermediate-2 genetic score and three points for a high risk genetic score.4 The CPSS-Mol stratifies patients into four categories, low (0 risk factors), intermediate-1 (1 risk factor), intermediate-2 (2–3 risk factors) and high (≥4 risk factors) risk, with median overall survival not reached, 64, 37 and 18 months; with 4-year leukemic transformation rates of 0%, 3%, 21% and 48%, respectively.7 Table 2 highlights relevant CMML-specific prognostic models along with their component variables. Recently a CMML transplant model was developed (CMML transplant score) which assigned four points for the presence of ASXL1 and/or NRAS mutations, four points for bone marrow blasts >2% and one point for each hematopoietic stem cell transplant (HSCT) comorbidity index, effectively stratifying for both overall survival and non-relapse mortality.68

In practice, any of the three molecularly integrated CMML prognostic models can be used for risk stratification. While these models have not been formally compared against each other, they share several overlapping prognostic features, especially anemia, elevated white blood cell counts and truncating ASXL1 mutations.4,51 I use both the MMM and the CPSS-Mol model for risk stratification at my institution.

How I manage patients with chronic myelomonocytic leukemia

The first step in the management of CMML patients is establishing an accurate diagnosis, followed by personalized risk stratification. Using any one of the molecularly integrated prognostic models, CMML patients can be stratified into lower risk and higher risk groups (Figure 4). Management strategies for these two risk groups are described below.

Lower-risk chronic myelomonocytic leukemia

I define lower-risk CMML patients as those who fall into low and intermediate-1 risk categories based on the MMM and the CPSS-Mol, or the low-risk category of the GFM model. On average these patients have a median overall survival of 60–100 months4,52 and the following treatment strategies can be adopted for their care:
Observation and supportive care. Several low-risk patients can be observed without any CMML-directed therapies, with serial blood count measurements and management of symptoms as needed. There are some data to suggest that in pCMML, permissive leukocytosis/monocytosis can be associated with increased lysozyme levels and a higher prevalence of chronic kidney disease (lysozyme nephropathy), and in select asymptomatic pCMML patients with white blood cell counts >30x10⁹/L, I do recommend hydroxyurea to control blood counts and proliferative features.⁶⁹ Side effects associated with hydroxyurea include nausea, vomiting, diarrhea, fever, mouth sores, photosensitivity, myelosuppression, and chronic non-healing leg/ankle ulcers.

Anemia. Ineffective erythropoiesis contributes to significant morbidity and mortality in CMML. While there are limited CMML-specific prospective data for anemia management, akin to MDS, the management of anemia largely centers around the use of red blood cell transfusions and erythropoiesis-stimulating agents. Extrapolating from MDS-based trials, in CMML, erythropoiesis-stimulating agents are also more likely to be effective in lower-risk patients, especially those with endogenous erythropoietin levels <200 U/L and those with low or no dependency on red blood cell transfusions (40-70% response rates).⁷⁰⁻⁷² The median duration of response to erythropoiesis-stimulating agents is 12-18 months, with limited options after progression. I usually use fixed doses of recombinant human erythropoietin or darbepoetin and strictly avoid the use of granulocyte – colony-stimulating factor) given the higher baseline risk of splenic rupture in CMML patients.⁷³ I closely monitor for adverse vascular side effects associated with erythropoiesis-stimulating agents, such as treatment-emergent hypertension and thromboembolism and do not administer these agents when hemoglobin levels are >11 g/dL. Luspatercept is a recombinant fusion protein that traps GDF11 and activin ligands belonging to the TGF-β superfamily, decreasing SMAD2 and SMAD3 signaling, enabling late-stage erythroid maturation and has been approved by the Food and Drug Administration for patients with β-thalassemia and MDS-ring sideroblasts.⁷⁴ While there are no clear safety or efficacy data on the use of luspatercept in CMML, I do consider off-label use in a select group of SF3B1-mutant CMML patients with bone marrow-ring sideroblasts, who are ineligible for erythropoiesis-stimulating agents or in whom these agents have failed.⁴³ Luspatercept is in general well tolerated with side effects including headaches, bone pain, arthralgia and fatigue. We have recently defined SF3B1 mutant CMML as a CMML subtype with predominant dysplastic features, with a low frequency of ASXL1 mutations, higher frequency of JAK2V617F mutations, concurrent splicing mutations, and a superior AML-free survival.⁴² Other options for anemia management include danazol (an anabolic steroid), lenalidomide (an immunomodulatory agent; note - isolated del5q is seen in <1% of CMML cases) and DNA methyltransferase (DNMT) inhibitors, such as 5-azacitidine, decitabine and oral decitabine combined with cedazuridine (cytidine deaminase inhibitor), given in either conventional doses, or in attenuated dose schedules.⁷⁶,⁷⁷ Given that these strategies for managing anemia are either suboptimal or not durable, I strongly encourage participation in clinical trials.
**Splenomegaly.** Symptomatic splenomegaly can be a significant issue in patients with pCMML. Clinical issues related to splenomegaly include early satiety, abdominal pain and tenderness, constitutional symptoms, referred shoulder pain, hiccoughs and mechanical obstruction of abdominal organs.^{72} Splenic infarction and spontaneous splenic rupture can result in abdominal catastrophes.^{73} I usually manage symptomatic splenomegaly, or massive splenomegaly, with cytoreductive therapy, with hydroxyurea being my first choice. There are recent encouraging data on the use of ruxolitinib, a JAK1/2 inhibitor, in patients with CMML, with 43% of CMML patients with baseline splenomegaly demonstrating a spleen response.^{78} Ruxolitinib was well tolerated with the two most common grade 3 and 4 treatment-related toxicities being anemia (10%) and thrombocytopenia (6%). I have used ruxolitinib off-label in select patients with good effect. DNMT inhibitors, splenic radiation and splenectomy are generally avoided, given inherent complications such as worsening cytopenias with DNMT inhibition, lack of durable responses with radiation and surgical morbidity/mortality associated with splenectomy.

**Thrombocytopenia.** Thrombocytopenia in CMML has diverse etiologies including splenic sequestration from hypersplenism, immune-mediated thrombocytopenia and bone marrow failure from progressive disease. Autoimmune phenomena, including immune-mediated thrombocytopenia, can be seen in 20-30% of CMML patients.^{79,80} While corticosteroids and rituximab have been used for patients with suspected immune-mediated thrombocytopenia, the use of thrombopoietin analogs, especially eltrombopag in CMML needs caution. There are reports of pCMML patients demonstrating worsening proliferative features, circulating blasts and bone marrow fibrosis on exposure to eltrombopag.^{81} The GFM however has completed a yet to be published phase II trial (NCT02323178) assessing the safety of eltrombopag in CMML patients with severe thrombocytopenia (platelet count <50x10^9/L). In this study eltrombopag was relatively well tolerated (median dose 150 mg; range, 100-300 mg), with 46.7% of patients achieving a platelet response (10 with dCMML and 4 with pCMML) that in general was not durable (median duration 3.4 months; range, 1.7-11.6 months). \( \text{I use extreme caution when prescribing eltrombopag for pCMML patients with proliferative features.} \)

Other options for thrombocytopenia include splenectomy when immune-mediated thrombocytopenia or splenic sequestration is suspected and DNMT inhibitors if the etiology is disease-related bone marrow dysfunction/failure.

**Autoimmune manifestations.** Autoimmune and systemic inflammatory manifestations such as erythema nodosum, leukocytoclastic vasculitis, Sweet syndrome, polymyalgia rheumatica, seronegative arthritis, and mixed connective tissue disorder-like syndromes can be seen in 20-30% of patients, with manifestations often preceding the diagnosis of CMML.^{79,80} With growing evidence on the role played by clonal hematopoiesis-clones in amplifying inflammation and endothelial dysfunction, there is more understanding on the pathobiology of inflammation and autoimmunity in CMML.^{82-84} Cytokines whose levels are elevated in CMML patients include, IL-8, IP-10, IL-1RA, TNF-\( \alpha \), IL-6, MCP-1/CCL2, HGF, M-CSF, VEGF, IL-4, and IL-2RA, with decreased levels of IL-10 being associated with adverse prognosis.^{85} The transcriptional signature of CMML monocytes is also highly inflammatory, with upregulation of multiple inflammatory pathways, including TNF-\( \alpha \), IL-6 and IL-17.^{86} While corticosteroids and steroid-sparing/disease-modifying agents are often used in the management of these symptoms, I use DNMT inhibitors in conventional or low doses, for more durable responses.^{80} Azathiprine is a steroid-sparing immunosuppressive agent that I strictly avoid, given its strong association with therapy-related myeloid neoplasms.

**Higher-risk chronic myelomonocytic leukemia**

I define higher-risk CMML patients as those who fall into intermediate-2 and high-risk categories based on the MMM and the CPSS-Mol, or the high-risk category of the GFM model. On average these patients have a median overall survival <2 years^{4,5,11} and the following treatment strategies can be adopted for their care.

**Allogeneic HSCT.** Allogeneic HSCT remains the only potentially curative option for patients with CMML. However, given the older age at presentation and associated morbidities, most patients are not eligible.^{87} At our institution, CMML patients with higher-risk disease diagnosed <75 years of age and with an acceptable HSCT-comorbidity index (deemed by an expert committee) are usually referred for allogeneic HSCT.^{88} A recent consensus document from an expert panel does recommend upfront allogeneic HSCT for intermediate-2 and high-risk CMML patients (CPSS risk stratification), with <10% bone marrow blasts.^{89} For patients with >10% bone marrow blasts, I usually cytoreduce with DNMT inhibition or AML-like induction therapy, especially in “younger and fit” patients.^{8,88} In the largest study to date, the European Group for Blood and Bone Marrow Transplant reported outcomes of 513 patients (median age 53 years) of whom 249 received myeloablative conditioning and 228 received reduced intensity conditioning.^{90} The 4-year non-relapse mortality was 41% and relapse rate 32%, accounting for a 4-year relapse-free survival rate of 27% and an overall survival rate of 33%.^{90} In this study the only factor prognostic for favorable outcomes was the achievement of a complete remission prior to HSCT. Data with regard to the use of DNMT inhibitors prior to HSCT in CMML are largely retrospective and somewhat controversial, given their lack of disease-modifying efficacy and propensity to worsen existing cytopenias.^{91} In general, I try to avoid DNMT in-
hinition prior to HSCT, unless it is needed to cytoreduce a patient prior to conditioning therapy. A recent Mayo Clinic study confirmed the survival benefit offered by allogeneic HSCT in higher-risk CMML patients, with 5-year overall survival rates of 51% for patients with chronic phase CMML and 19% for those with blast transformed CMML. Soberingly the graft-versus-host disease relapse-free survival in the chronic phase cohort was only 7 months. With a greater availability of donor sources, alternative donor transplant strategies and an improving arsenal for management of graft-versus-host disease, we hope that allogeneic HSCT becomes a viable option for a greater number of patients.

DNMT inhibitors. DNMT inhibitors such as 5-azacitidine, decitabine and the oral combination of decitabine with cedazuridine are the only drugs approved for the management of CMML by the U.S Food and Drug Administration. In Europe, 5-azacitidine remains the only drug approved for the management of CMML (>10% blasts). The approval of these agents was largely based on MDS predominant trials that included a small number of CMML patients, all of whom had a white blood cell count <12x10^9/L (dCMML). The overall response rates to DNMT inhibitors are approximately 40-50%, with true complete remission rates of <20%. In a seminal study, elaborate sequencing data demonstrated that DNMT inhibitors induce responses in CMML patients by epigenetically restoring normal hematopoiesis, without impacting mutational allele burdens, with disease progression to AML remaining inevitable. The struggle with using DNMT inhibitors in CMML is the lack of predictors or biomarkers of response. In a recent prospective randomized trial assessing the efficacy of decitabine versus hydroxyurea in higher-risk pCMML patients (n=170), there was no difference in overall survival or event-free survival between the hydroxyurea and decitabine arms (NCT02214407; Itzykson et al. ASH 2020). Adverse effects of DNMT inhibitors include nausea, vomiting, diarrhea, fatigue, and myelosuppression. I proactively educate my patients about these adverse effects and optimize supportive care for the preemptive management of the same.

I largely use DNTM inhibitors in dCMML subtypes with higher risk disease or clinically significant cytopenias, especially if they are TET2 mutant and ASXL1 wildtype (Figure 5). I avoid using DNMT inhibitors in pCMML patients with dominant RAS pathway mutations or with highly proliferative features. For these patients I proactively seek clinical trials with novel therapeutic agents. For patients who respond to DNMT inhibition, the median duration of re-
sponse is 12-18 months and survival after progression is dismal, ranging between 6-9 months. Given recent data suggesting improved survival rates in AML patients treated in combination with azacitidine and the bcl-2 inhibitor venetoclax, there has been interest in assessing this combination in CMML. Preclinical BH3 mimetic profiling data in CMML suggest that the malignant monocytes are addicted to mcl1 instead of bcl2 and that combination therapy with mcl1 and MAPK inhibitors might be a successful treatment strategy. While prospective data are awaited, a small retrospective series including CMML patients with blast transformation demonstrated suboptimal response rates (overall response rate - 50% for CMML), with no significant difference from response rates seen with DNMT inhibitors alone.

**Clinical trials.** I actively seek out clinical trials for all our CMML patients, given the suboptimal response rates to conventional strategies. We have successfully carried out CMML-specific clinical trials and urge the scientific community to stop grouping CMML with MDS or MPN, given the unique biology of CMML. CMML-specific trials that have been completed or are currently accruing include trials assessing the safety and efficacy of lenzilumab (an anti-GM-CSF monoclonal antibody: NCT02546284), tipifarnib (a farnesyl transferase inhibitor: NCT02807272), ruxolitinib (a JAK1/2 inhibitor: NCT03722407), cobimetinib (a MEK inhibition: NCT04409639) and tagraxofusp (a protein conjugate involving IL-3 and truncated components of the diphertheria toxin: NCT02268253) in patients with CMML.

Preclinical data from our laboratory have demonstrated a unique RAS-KMT2A-PLK1 axis defining the pCMML phenotype, with PLK1 inhibition with the oral, selective PLK1 inhibitor onvansertib demonstrating excellent preclinical activity.

**Conclusions**

CMML is a unique MDS/MPN overlap neoplasm with relative genetic homogeneity, but with marked clinical heterogeneity. The disease is seen in the elderly and frequently develops on the background of clonal hematopoiesis, with recurrent somatic mutations involving TET2, ASXL1, SRSF2 and the RAS pathway defining dysplastic and proliferative subtypes of CMML. For several years CMML was considered as a subtype of MDS, but from 2002 onwards, CMML has been rightfully recognized as a unique neoplasm with the development of CMML-specific prognostic models, response criteria, preclinical models and, most importantly, clinical trials; heralding a new future for this disease and affected patients. Several challenges remain, including the lack of uniform consensus on personalized prognostication and more importantly, the identification of disease-modifying targets and therapies that might ameliorate disease progression, improve quality of life, and potentially offer a cure.

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