The Clinical Management of Chronic Myelomonocytic Leukemia

Eric Padron, MD, Rami Komrokji, and Alan F. List, MD

Dr Padron is an assistant member, Dr Komrokji is an associate member, and Dr List is a senior member in the Department of Malignant Hematology at the H. Lee Moffitt Cancer Center & Research Institute in Tampa, Florida.

Address correspondence to:
Eric Padron, MD
Assistant Member
Malignant Hematology
H. Lee Moffitt Cancer Center & Research Institute
12902 Magnolia Drive
Tampa, Florida 33612
E-mail: eric.padron@moffitt.org

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Abstract: Chronic myelomonocytic leukemia (CMML) is an aggressive malignancy characterized by peripheral monocytosis and ineffective hematopoiesis. It has been historically classified as a subtype of the myelodysplastic syndromes (MDSs) but was recently demonstrated to be a distinct entity with a distinct natural history. Nonetheless, clinical practice guidelines for CMML have been inferred from studies designed for MDSs. It is imperative that clinicians understand which elements of MDS clinical practice are translatable to CMML, including which evidence has been generated from CMML-specific studies and which has not. This allows for an evidence-based approach to the treatment of CMML and identifies knowledge gaps in need of further study in a disease-specific manner. This review discusses the diagnosis, prognosis, and treatment of CMML, with the task of divorcing aspects of MDS practice that have not been demonstrated to be applicable to CMML and merging those that have been shown to be clinically similar.

Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal hematologic malignancy characterized by absolute peripheral monocytosis, ineffective hematopoiesis, and an increased risk of transformation to acute myeloid leukemia. This entity has been recognized since its initial description by G. Stewart Smith in 1937 and formally defined by the French-American-British (FAB) group in 1978 as 1 of the 5 inaugural subcategories of myelodysplastic syndromes (MDSs).[1,2] In addition to the initial classification of CMML, the FAB group subclassified CMML into an MDS-CMML group if the white blood cell (WBC) count is less than 13.0×10^9/L and a myeloproliferative neoplasm (MPN)-CMML group if the WBC count is 13.0×10^9/L or greater.[2] Since this designation, debate over whether CMML should be better classified as an MDS or an MPN has resulted in a dynamic ontologic history.[3] Recent advances in DNA sequencing have allowed for the near-complete annotation of gene mutations in CMML and have uncovered a unique genomic

fingerprint that characterizes this disease. There appears to exist a particular diverse set of recurrent mutations that are predicted to affect divergent cellular processes such as receptor signaling, alternative splicing, and chromatin modification.[4-7] Although there is no single "CMML-defining" genetic event, the unique frequencies of select mutations in this disease are striking and confirm that it is indeed an MDS-independent entity.

To this end, the World Health Organization classified CMML within a provisional category in 2001, later formalized in 2008, containing hematologic malignancies with features overlapping myeloproliferative syndromes and MDSs by creating a novel designation known as the myelodysplastic/myeloproliferative neoplasms (MDS/MPNs).[8] This group is shared by 3 other related diseases: juvenile myelomonocytic leukemia, a pediatric disease with a clinical phenotype similar to that of CMML; atypical chronic myeloid leukemia; and MDS/MPNs unclassifiable. A provisional entity known as refractory anemia with ringed sideroblasts with associated thrombocytosis (RARS-T) has also been included. Clinical research on CMML, because of its previous association with MDSs, has been historically performed under the umbrella of more global MDS investigation. As such, a critical task for the CMML clinician is to unravel which principles of "MDS clinical practice" truly apply to CMML and which are only true for MDSs (Table 1). Although the bulk of "CMML clinical practice" is inferred from MDS data, recent clinical data are becoming increasingly available to help formulate an evidence-based approach to the clinical management of CMML. Herein we review the clinical management of this disease and discuss clinical controversies that have arisen from its historical classification as a subtype of MDSs.

Table 1. Clinically Significant Features of MDS vs CMML

	MDS	CMML
Cytopenias present	Yes	Yes
Splenomegaly present	No	Yes (50% of cases)
Constitutional symptoms	Rare	Yes (frequency unknown)
AML transformation rate	30% of cases	30% of cases
Median survival	30 months	12-19 months
Preferred prognostic tool	IPSS/IPSS-R	Unknown
Treatment options --Hematologic improvement --Splenomegaly --Disease modification	 HMA, lenalidomide NA Azacitidine	 HMA Hydroxyurea, topotecan None
Stem cell transplant options	Allogeneic	Allogeneic

CMML, chronic myelomonocytic leukemia; HMA, hypomethylating agents; IPSS, International Prognostic Scoring System; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; NA, not applicable.

Diagnosis

A diagnosis of CMML can be suspected when persistent, unexplained peripheral monocytosis is present in an older adult.[9] Additional cytopenias are usually present at the time of diagnosis, however, and splenomegaly is seen in approximately 50% of cases.[10] A bone marrow biopsy and aspiration are absolutely required and should include karyotype analysis by conventional cytogenetics and fluorescence in situ hybridization if no dividing cells are present for G-banding analysis. Cytogenetic abnormalities are detected in less than 30% of cases; trisomy 8 is the most frequent of these.[11] The bone marrow aspirate should demonstrate morphologic dysplasia as defined in the diagnostic algorithm for MDSs but, unlike with MDSs, this is not absolutely required for the diagnosis of CMML.[8] An elevated ratio of myeloid to erythroid cells is often identified in the bone marrow aspirate as are atypical, characteristic monocytes known as paramyeloid cells.[12] Myeloblasts and promonocyte in the bone marrow and peripheral blood must be less than 20%.

According to the World Health Organization 2008 classification, a diagnosis of CMML requires persistent monocytosis of greater than 1.0×10^9/L, with persistence loosely defined as lasting longer than 3 months. In patients with extremely elevated leukocyte counts, the monocytes should account for greater than 10% of the WBC differential. Cases are further subdivided into CMML-1 (<5% peripheral blasts and promonocytes, <10% bone marrow blasts and promonocytes) and CMML-2 (5%-19% peripheral and 10%-19% marrow blasts and promonocytes).[8,13] Other myeloid malignancies should be considered, with special attention placed on the exclusion of chronic myeloid leukemia by screening for *BCR-ABL* gene fusion. Rearrangements of *PDGFRA* or *PDGFRB* must be excluded in cases of CMML with eosinophilia, as these molecular lesions identify other well-described hematologic malignancies with sensitivity to imatinib (Gleevec, Novartis).[14] If no clonal marker is identified and no dysplasia appreciated on morphologic examination, the diagnosis of CMML can be made in patients with monocytosis alone. This clinical situation is not uncommon, as many patients with true CMML have only minimal dysplasia and no cytogenetic lesion.[15] However, if one wishes to make the diagnosis of CMML based on monocytosis alone, all other causes of monocytosis must be excluded, including aggressive solid tumors, infectious etiologies, and autoimmunity. The last can be problematic, as preliminary data exist suggesting an association between true

CMML and autoimmune disease.[16] Several techniques can be useful to assist in diagnosis in the patient with persistent monocytosis and the absence of dysplasia. Single nucleotide polymorphism array allows for the detection of cryptic copy number changes that can be indicative of clonality and identify a microchromosomal deletion unidentified by cytogenetics or fluorescence in situ hybridization.[17] Target enrichment of known recurrently mutated genes annotated with next-generation or Sanger sequencing can also identify low-frequency mutations that can establish clonality and guide in the diagnosis and assessing the prognosis of CMML.[4]

Incidence and Epidemiology

The median age of presentation is 65 to 75 years, with a male predominance. The exact prevalence of CMML is unknown, but 2 large epidemiologic studies estimate that CMML constitutes approximately 10% of all cases of MDSs.[18] Unlike with MDSs, therapy-related CMML is a rare event that has been historically reported in small cases series.[19] A recent report derived from a large single-institution cohort identified a therapy-related CMML frequency of 11% along with worse overall survival.[20] Although underrepresented because of the poor standardization in CMML coding, the age-adjusted incidence of CMML in the United States is 0.3 per 100,000 using data extracted from the SEER (Surveillance, Epidemiology, and End Results) program registry as of 2004.[18] A recent analysis estimating the incidence of myeloid malignancies in a Spanish population reported a CMML incidence of 0.39 per 100,000, which was comparable to the incidence of refractory anemia with ringed sideroblasts (RARS) and primary myelofibrosis.[21] Although juvenile myelomonocytic leukemia occurs in infancy and is uniformly associated with mutations that alter Ras signaling, no hereditable CMML syndromes have been reported.[10] Familial cases of mutations associated with CMML have been reported as with Runt-related transcription factor 1 (RUNX1) in familial platelet disorder, but these patients tend to develop a classic MDS.[22]

Prognosis

The prognosis of patients with CMML is poor overall, with a median survival of only 20 to 30 months and leukemic transformation rates of 15% to 20%.[4,20,23,24] These survival rates compare unfavorably to MDS survival rates, suggesting that CMML is a more aggressive disease.[18] However, significant heterogeneity exists among patients with CMML, and risk stratification is critical for the estimation of prognosis and treatment decisions for the individual patient. Deciding which prognostic model to employ in a CMML patient is difficult. One reason for this difficulty is that more than 8 prognostic scoring tools are now available.[4,23-30] Many of these tools have been externally validated in CMML cohorts but their relative prognostic power has not been compared, making it difficult to recommend any one CMML-specific prognostic tool over another. Another reason is that prognostic models for CMML have traditionally incorporated predictors of survival biased toward MDS patients. This makes the wide application of some models to CMML problematic and, in some cases, inappropriate.

The most widely used model for the prognostication of MDSs and CMML is the International Prognostic Scoring System (IPSS) published in 1997, and more recently updated and reported as the revised IPSS (IPSS-R).[25,26] Although the entire MDS cohort used to formulate the prognostic model was very large, the IPSS study included only 126 patients with CMML and specifically excluded CMML patients with a WBC count of greater than 12 × 10^9/L, making this model suboptimal for patients with proliferative disease.[26] The IPSS-R study did have a significantly larger CMML cohort and an MDS cohort of more than 7000 patients, but again excluded CMML patients with a WBC count of greater than 12 × 10^9/L.[25] Nonetheless, the IPSS and IPSS-R remain the most widely used prognostic tools for CMML in practice and in clinical trials. Their wide use also can be partially attributed to the fact that prognostication is based on 3 readily available parameters: number of cytopenias, percentage of myeloblasts in the bone marrow, and G-band karyotyping. The IPSS-R refines the bone marrow blast percentage value and depth of cytopenias, improving its prognostic power in MDS patients. However, the IPSS-R has not been formally externally validated in CMML patients, nor has it been compared with the IPSS in the context of CMML.

A second widely used model, the global MD Anderson scoring system, has also been translated to CMML. In this model, prognostic factors include performance status (≥2), age (60-64 and ≥65 years), platelet count (<30, 30-49, 50-199 × 10^9/L), hemoglobin (<12 g/dL), percentage of bone marrow blasts (5%-10% and 11%-29%), WBC count of greater than 20 × 10^9/L, karyotype, and prior transfusion on a weighted scale.[27] This model is able to refine the precision of the IPSS in MDSs and is more applicable to patients with CMML because proliferative-type CMML patients were not excluded from analysis. In a preliminary study, the MD Anderson scoring system tended to outperform other CMML models. However, the global MD Anderson model requires many factors for risk stratification, making it difficult to apply to all patients and cumbersome for community-based practitioners.[31]

Table 2. Historical CMML-Specific Prognostic Tools

Study	N (total)	n (CMML)	Treatment	CMML Validation	Cytogenetics Considered	Genetics Considered
MDAPS	213	213	Yes[a]	Germing[32]	No	No
DS	235	25	No	Padron, Germing[31,32]	No	No
SS	70	70	Yes[b]	Padron, Germing[31,32]	No	No
mBS	53	53	No	Germing[32]	No	No

CMML, chronic myelomonocytic leukemia; DS, Düsseldorf score; mBS, modified Bournemouth score; MDAPS, MD Anderson Prognostic Score for CMML; MDS, myelodysplastic syndrome; SS, Spanish score.

Modified with permission from Padron et al. *J Clin Oncol*. 2013;31(19):2374-2376.[34]

[a] Patients received either supportive care (n=71), α- or γ–interferon (n=9), low-dose or single-agent chemotherapy, or intensive chemotherapy (n=65).

[b] 35% of patients received low-dose cytarabine, hydroxyurea, or mercaptopurine.

Lastly, a 1992 prognostic score developed in Düsseldorf, Germany, stratified 235 MDS patients into low-risk, intermediate-risk, and high-risk groups. This system incorporates anemia (hemoglobin ≤9 g/dL), elevated lactate dehydrogenase, thrombocytopenia (platelet count ≤100 × 10^9/L), and marrow blast levels of 5% or greater.[28] This score has been validated in a hypomethylating agent–naive CMML cohort and a hypomethylating agent–treated CMML cohort, and is of particular note because it can identify a low-risk population of patients with indolent CMML, who rarely require therapy.[32]

Several early CMML-specific prognostic tools have been developed in conjunction with the IPSS in MDSs that attempt to look at risk stratification of a CMML-specific cohort.[28-30,33] These models laid the framework for modern CMML tools and are summarized in Table 2. Three recent CMML-specific models have been developed that build on the summarized classic CMML-specific prognostic models; each represents advances in the risk stratification of the disease. The first reported modern CMML model was developed by the Spanish MDS cooperative group. This prognostic model was derived from a cohort of 558 patient and identified chromosome abnormalities, red blood cell transfusion dependence (or anemia), bone marrow blast count, and WBC count as independently associated with poor survival.[23] This model highlighted that chromosomal abnormalities are prognostic in CMML, as they are in MDSs, a finding previously reported by the same group.[11] It further highlighted that the molecular characteristics of prognosis of CMML are different than those of MDSs, as trisomy 8 was specifically prognostically adverse in CMML and not known to be so in MDSs.

Another recent model developed in the United States from a cohort of 226 CMML patients at the Mayo Clinic identified an increased peripheral monocyte count (>10 × 10^9/L), the presence of circulating immature myeloid cells, decreased hemoglobin (<10 g/dL), and decreased platelet count (<100 × 10^9/L) as prognostic of overall survival. This model highlights the prognostic impact of monocytes, can be calculated from only a complete blood cell count with differential, and was externally validated in an independent CMML cohort at the H. Lee Moffitt Cancer Center & Research Institute.[24] Lastly, the most recent model proposed by the GFM group (Groupe Francophone des Myélodysplasies) tested the significance of both clinical parameters and known genetic mutations in a cohort of 312 patients in France. Here, a prognostic model was derived that included the presence of *ASXL1* mutations, patients older than 65 years, WBC counts of greater than 15 × 10^9/L, platelet counts of less than 100 × 10^9/L, and anemia (hemoglobin <10 g/dL in female patients, <11 g/dL in male patients).[4] It represents the first CMML-specific model that incorporates gene mutations, has been extensively internally and externally validated, and outperforms several prognostic models with clinical parameters alone.[34]

Other Prognostic Features of CMML

In MDSs, the presence of anemia, dysplasia in the erythroid lineage, and more than 15% ringed sideroblasts in the bone marrow erythroid precursors without elevations in myeloblast percentage are diagnostic of RARS. Prior studies have shown that the RARS subtype of MDSs is particularly indolent and portends a good prognosis, but data from the Spanish MDS group presented in abstract form demonstrate that ringed sideroblasts may also have prognostic significance in CMML. Such and colleagues examined 77 patients with CMML with greater than 15% ringed sideroblasts (CMML-RS) in the bone marrow at presentation and compared these patients with 417 patients who had "classical CMML" (<15% ringed sideroblasts) and 178 patients who had classical RARS. Patients with CMML-RS had significantly better overall survival than patients with classical CMML, as well as a lower risk of evolution to acute leukemia.[35]

Treatment Options

The treatment armamentarium for CMML continues to be limited by the lack of CMML-specific clinical trials. Owing to inferences made from advances in the treatment of MDSs, the treatment of CMML has progressed from cytotoxic chemotherapy with high toxicities and low response rates, with agents such as etoposide and hydroxyurea, to hypomethylating agents with higher response rates and lower toxicity profiles. However, it remains critically important to understand which elements of MDS therapeutic principles are translatable to CMML. For instance, practice guidelines and retrospective analyses have established that low-risk, asymptomatic MDS patients are unlikely to benefit from treatment and that high-risk MDS patients should be treated with azacitidine, as it prolongs overall survival.[36] Although it is tempting to adopt this treatment algorithm in CMML, little evidence is available to support this translation. Despite the efficacy of hypomethylating agents, there remains no disease-modifying therapy for CMML. The only known disease-modifying therapy in patients with CMML is allogeneic stem cell transplant (ASCT). Unfortunately, most patients with CMML are not candidates for this therapy because of multiple comorbidities and/or advanced age. Nonmyeloablative conditioning regimens have allowed a larger minority of CMML patients to undergo ASCT.

A second critical differentiator of CMML from MDSs is that myeloproliferative features should be considered in the treatment decisions, as these can account for significant morbidity. Unlike MDS patients, CMML patients can present with splenomegaly in 50% of cases, with serious sequelae including early satiety and intractable pain. It is in these cases that cytoreductive therapies detailed below are used in an attempt to improve these serious symptomatologies.[37] Further, it is our experience that, although poorly described in the literature, myelofibrosis-like constitutional symptoms are occasionally seen in patients with CMML. Although clinical trials are always the preferred option for these patients, cytoreductive therapies may have an impact on severe constitutional symptoms similar to that in myelofibrosis patients.

Hematopoietic Stem Cell Transplantation

Several studies have addressed the impact of ASCT on CMML. All studies enrolled patients who were younger than the median age of patients at the time of CMML diagnosis and who had excellent performance status. In the largest reported cohort, from the Fred Hutchinson Cancer Research Center, 85 CMML patients were followed for up to 19 years. Predominantly using reduced-intensity conditioning regimens the authors found a 10-year progression-free survival rate of 38% and a 10-year relapse incidence of 27%. Mortality was reported to be negatively correlated with pretransplant hematocrit, high-risk cytogenetics, higher hematopoietic stem cell transplantation comorbidity index, and increased age.[38] A second French study reported transplant outcomes for 73 patients who underwent reduced-intensity conditioning. Similar progression-free survival and relapse incidence were reported. Interestingly, the only clinical variable associated with poor outcomes in this study was the presence of palpable splenomegaly at time of transplant.[39] These referenced studies are in concordance that long-term survival curves plateau, which suggests that some patients can be cured of their disease. Despite data suggesting potentially curative therapy in select CMML cases, significant toxicity associated with ASCT prevents the widespread adaptation of this technology to all cases of CMML.[40,41] Indeed, the decision to use transplantation and its timing in an individual CMML patient remain undefined. Patient-specific exclusions such as comorbidities or age are more straightforward, but determining which CMML patients to recommend for ASCT is difficult. For MDS patients, Markov decision models exist for determining the optimal timing of ASCT[42,43]; they suggest that higher-risk MDS patients benefit most from early transplant, whereas lower-risk patients gain quality life-years by delaying this procedure. Substantial evidence regarding the natural history of CMML as it compares with MDSs suggests that these decision models should not be applied to CMML. Firstly, CMML is an overall more aggressive disease compared with MDSs, such that it is conceivable that every patient with CMML be considered for transplant. Second, even if a population exists that would not benefit from transplant, no data exist to guide clinicians as to what prognostic model to choose to risk-stratify patients prior to transplant. Preliminary data do exist that are beginning to address this, but many more studies are required to answers these critical clinical questions.

Pharmacologic Therapies in CMML

Conventional cytotoxic therapies have had only modest activity in CMML. However, several studies have reported the efficacy of the topoisomerase inhibitors topotecan and etoposide. Topotecan, both as single-agent therapy and in combination with cytarabine, was found to have activity in patients with CMML in multiple studies performed at the MD Anderson Cancer Center.[44] Other early small trials examined the use of etoposide and all-*trans*-retinoic acid (ATRA). Cambier and colleagues found that ATRA could improve the anemia and thrombocytopenia in patients with advanced CMML, but could also induce hyperleukocytosis.[45] However, the disease-modifying capacity of the topoisomerase inhibitors came into question when Wattel and colleagues published the results of

a randomized trial of 105 patients with CMML in which patients were randomly assigned to receive hydroxyurea or etoposide. This trial showed a statistically significant improved median overall survival of 20 months in the hydroxyurea group compared with 9 months in the etoposide arm, suggesting that there is little disease-modifying evidence for etoposide in CMML.[46]

The identification of hypomethylating agent has transformed the clinical management of MDS. However, as has occurred in the clinical history of CMML, the hypomethylating agents azacitidine and decitabine were approved by the US Food and Drug Administration for the treatment of CMML. Despite only limited data from randomized studies, the hypomethylating agents are the universal first-line pharmacologic agents in CMML. In 2002, azacitidine was studied by Silverman and colleagues in a randomized, controlled trial in MDS patients, of whom 14 had CMML.[47] Of the patients in this study, 37% had hematologic improvement compared with 6% in the supportive care arm. The authors also found improved median overall survival in the azacitidine arm when compared with supportive care (20 months vs 14 months).[47] Subsequently, Fenaux and colleagues published a phase 3, international, multicenter, parallel-group study of 358 patients with higher-risk MDSs (16 of whom had CMML), and found that treatment with azacitidine increased overall survival in this patient population when compared with conventional care that included best supportive care, induction therapy, and low-dose cytarabine.[48] Unfortunately, the CMML cohort was too small to conclude there was improved overall survival with azacitidine in subset analysis. In 2010, Costa and colleagues completed a phase 2 trial in 38 patients with CMML, which found that azacitidine was active in CMML with acceptable therapy-associated toxicity.[49] Oral azacitidine has also shown promise in the treatment of CMML in a recent phase 1 study, in which clinical responses were seen in 35% of previously treated MDS and CMML patients, and in 73% of patients receiving oral azacitidine as first-line therapy.[50] Decitabine has been examined in multiple phase 2 trials, with varied results. Several prospective studies have found response rates ranging from 10% to 58% in patients with CMML receiving decitabine.[51,52] Braun and colleagues conducted a phase 2 trial of 39 patients with severe CMML receiving decitabine, and reported a complete response rate of 10%, an overall response rate of 38%, and a 2-year overall survival rate of 48%. This study also found that lower *JUN* and *MYB* levels independently predicted improved overall survival, whereas mutations in *ASXL1*, *TET2*, *AML1, NRAS, KRAS, CBL, FLT3*, and *JAK2* genes had no statistical significance.[53] Other reports have demonstrated that *TET2* mutation, platelet doubling after the first cycle of therapy, and the MDS-CMML subtype by FAB criteria (defined as CMML patients with a WBC count of $<13 \times 10^9$/L) is predictive of response to hypomethylating agents.[54-58] In summary, prospective phase 2 study data after the US Food and Drug Administration approved azacitidine and decitabine to treat CMML have demonstrated that hematologic response rates are comparable to those in MDS patients. However, there are no data demonstrating a survival advantage with these agents in CMML.

Conclusion

CMML is an aggressive myeloid malignancy for which dramatic advances have been made in clinical management. Although most of these were inferred from MDS clinical research, subsequent research has validated the activity of hypomethylating agents in CMML and the applicability of several MDS-specific prognostic models. It is imperative for the CMML clinician to be able to separate MDS data that are applicable to CMML from those that are not. Several novel CMML-specific treatment approaches are now in clinical study that range from JAK2 to MEK inhibition.[59,60] Data from these trials will allow for the prospective annotation of clinical and genetic markers as well as identify critical cellular dependencies that could be used in combination with hypomethylating agents. It is our recommendation that every CMML patient be considered for clinical trials irrespective of risk stratification or treatment history because of limited prospective clinical data and the disease's aggressive natural history. Important clinical studies addressing these issues are under way, and more are anticipated.

Disclosures

The authors have no real or apparent disclosures to report.

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