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MYELOPROLIFERATIVE NEOPLASMS (B STEIN, SECTION EDITOR)

Chronic Myelomonocytic Leukemia: 2018 Update to Prognosis and Treatment

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Abstract

Purpose of Review Chronic myelomonocytic leukemia (CMML) is a rare and often aggressive myeloid malignancy. Historically, prognostic markers and therapeutic paradigms have been applied from myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPNs). Interest has increased recently in developing tailored approaches for the MDS/MPN *overlap* syndrome of CMML.

Recent Findings Multiple prognostic scores have been validated specifically for CMML in the past 5 years. These incorporate somatic mutations, with *ASXL1* mutations repeatedly correlating with poor prognosis. Accurate prognostication can guide treatment. Hypomethylating agents (HMAs) and curative allogeneic blood or marrow transplantation (BMT) remain the most available standard treatments. Recently, a number of novel approaches using unapproved therapies (i.e., lenalidomide, ruxolitinib, sotatercept, and tipifarnib) have demonstrated some efficacy in CMML.

Summary Increased recognition and interest in CMML have led to the development of a number of new prognostic models and potential treatment options. Standard treatment options remain limited and clinical trials should be strongly considered whenever available.

Keywords Chronic myelomonocytic leukemia (CMML) · Mayo prognostic model · CPSS · *ASXL1* · Hypomethylating agents · Allogeneic BMT

Introduction

Chronic myelomonocytic leukemia (CMML) is a disease of the hematopoietic stem cells characterized by features of both myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs). It is, thus, designated as an MDS/MPN overlap syndrome. The annual incidence of CMML is only 0.3 per 100,000, which makes designated clinical trials and prognostic scores difficult to establish. Because of this, CMML is often treated along with MDS or MPN paradigms. Recent efforts have attempted to improve understanding of CMML and establish disease-specific treatment paradigms to improve outcomes which, historically, are quite poor [1].

Clinical Features

Clinical Presentation

CMML typically affects older adults, above 65 years of age with a slight male predominance [1]. The clinical presentation of CMML includes features of both MDS and MPNs. Findings on complete blood count (CBC) may include leukocytosis (with monocytic predominance), anemia, and thrombocytopenia. Clinical manifestations include constitutional symptoms such as weight loss or night sweats, infections, fatigue, bleeding, and splenomegaly [2]. Circulating blasts may be present and, with time, CMML may progress to acute myeloid

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leukemia (AML). Less commonly, CMML may result in autoimmune complications, coagulopathies, gingival infiltration, skin rashes, hypokalemia, and creatinine elevation [2]. Therapy must factor in resultant comorbidities of this experienced age group of patient as well ensure symptom management in addition to the blood count irregularities. Prognosis and goals can vary widely for individual patients with this disease.

Somatic Mutations and Pathogenesis

Recent studies have focused on somatic mutations as drivers of pathogenesis in myeloid malignancies with the goal of better biologic understanding of the diseases in order to rationally predict clinical outcomes and tailor therapies for patients. In CMML, an initial "driver mutation" may occur in the hematopoietic stem cells, yielding a survival advantage for a clonal myeloid population [3]. With time, "clonal evolution" occurs such that additional lesions accumulate. The occurrence of a critical lesion or combination of lesions results in disruption of normal hematopoiesis and progression to the CMML phenotype [3–7]. Over 90% of CMML cases possess at least one somatic mutation, usually affecting genes responsible for epigenetic modification, mRNA splicing, transcription, and cell signaling (Fig. 1) [7–12]. Mutations in *SRSF2*, *TET2*, and *ASXL1* are particularly common in CMML [6•, 9, 10, 13, 14]. While the clinical utility is evolving, the mutational profile is proving useful to confirm diagnosis and predict prognosis and response to therapy and should be considered now a standard diagnostic procedure at the time of diagnosis [10, 15–17].

Diagnostic Criteria

When suspected, a diagnosis of CMML may be confirmed via peripheral blood (PB) and bone marrow (BM) biopsy with aspirate. Historically, patients were classified as either having MDS or MPN subtypes, depending on having a white blood cell count (WBC) less than or greater than 13×10^9/L, respectively [18]. The World Health Organization (WHO) diagnostic criteria were recently updated in 2016 (Table 1) [15]. In this current iteration, a diagnosis of CMML requires persistent peripheral blood monocytosis $\geq 1 \times 10^9$/L making up greater than 10% of the total WBCs, exclusion of other etiologies, and the presence of dysplasia. In the absence of dysplasia, the diagnosis may still be made in the presence of characteristic clonal genetic abnormalities and/or persistence of the monocytosis for at least 3 months without an alternate etiology. Notably, the presence of characteristic genetic lesions in isolation is not adequate to confirm CMML. Such findings may occur in healthy older patients with clonal hematopoiesis of indeterminate potential (CHIP) or clonal cytopenias of undetermined significance (CCUS) [15]. When CMML is confirmed, the diagnosis is further subclassified based on the presence of blasts as CMML-0 (PB blasts < 2%, BM blasts < 5%), CMML-1 (PB blasts = 2–4%, BM blasts = 5–9%), or CMML-2 (PB blasts = 5–19%, BM blasts = 10–19%). Blast percentages of 20% or higher in either compartment are consistent with AML [15, 19].

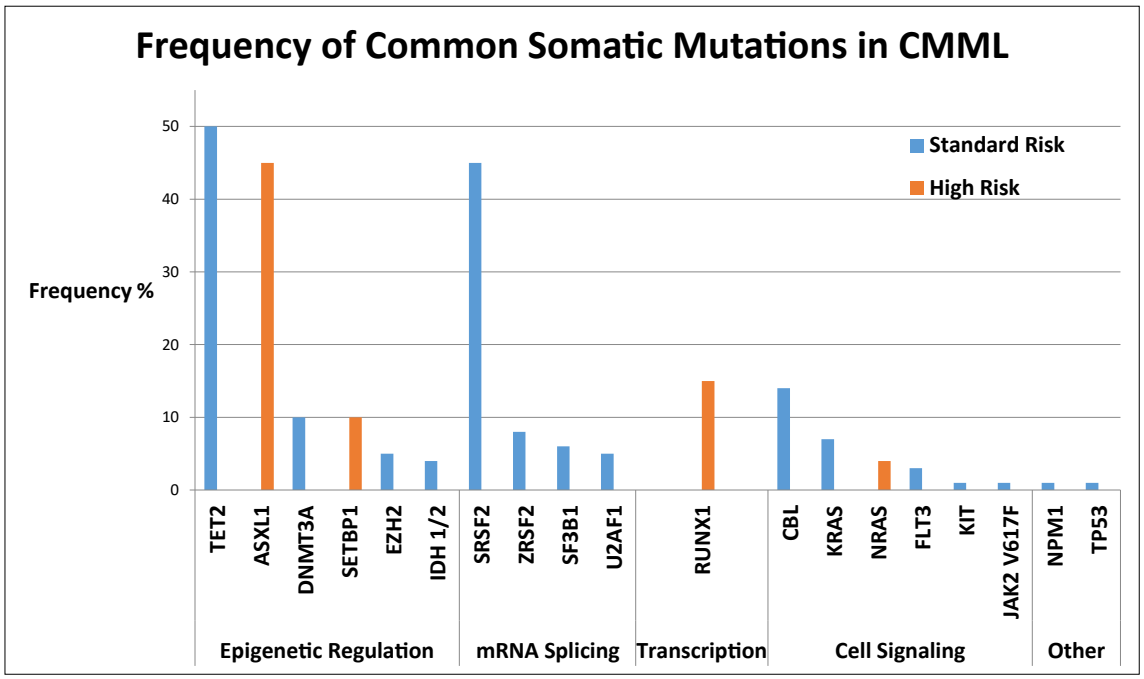

Fig. 1 Frequency of common mutations in CMML. High-risk mutations are denoted by an orange bar. (Data based on references 6•, 9, 10, 13–17)

Table 1 Updated CMML Diagnostic Criteria from the revised 2016 World Health Organization classification of myeloid neoplasms [15]

CMML diagnostic criteria
• Persistent PB monocytosis $\geq 1 \times 10^9$/L, with monocytes accounting for ≥ 10% of the WBC count
• Not meeting WHO criteria for *BCR-ABL1*$^+$ CML, PMF, PV, or ET
• No evidence of *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangement or *PCM1-JAK2* (should be specifically excluded in cases with eosinophilia)
• < 20% blasts in the blood and bone marrow
• Dysplasia in 1 or more myeloid lineages. If myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if the other requirements are met and
• An acquired clonal cytogenetic or molecular genetic abnormality is present in hematopoietic cells
OR
• The monocytosis (as previously defined) has persisted for at least 3 months
• All other causes of monocytosis have been excluded

Prognostic Models

Typically, CMML has an unfavorable prognosis with a median overall survival (OS) of approximately 3 years [20]. However, there is considerable heterogeneity in the clinical course with some patients progressing in months and others surviving many years with stable disease. Thus, accurate prognostic scores are critical to stratify patients in order to apply appropriate treatment paradigms and remain an ongoing challenge at bedside. Historically, models validated more specifically for MDS were applied to CMML, such as the international prognostic scoring system (IPSS) and the revised IPSS (IPSS-R), though specific CMML models such as the M.D. Anderson Prognostic System (MDAPS) are available [21–26]. Recent years have seen an eruption in CMML specific prognostic models, many of which have incorporated somatic mutations to better refine their predictive value (Table 2). Though many scoring systems are now available, none has emerged as clearly superior to date [27•, 28].

Mayo Prognostic Model

In 2013, a multi-institutional effort led by the Mayo Clinic established a new CMML prognostic score called the "Mayo Prognostic Model" [29]. The study evaluated 226 patients with CMML with a median age of 71 years. Median survival was 22 months for CMML-1 and 14 months for CMML-2. Significant variables that predicted survival were absolute monocyte count (AMC) > 10×10^9/L, presence of circulating immature myeloid cells (IMC), Hgb < 10 g/dL, and Plts < 100×10^9/L. Notably, evaluated somatic mutations had no impact on OS. The model stratified patients into low risk (0 risk factors) with median OS of 32 months, intermediate risk (1 risk factor) with median OS of 18.4 months, and high risk (≥ 2 risk factors) with median OS of 10 months. The risk categories also were predictive of leukemic transformation, a useful discussion point that patients value in consultation. The authors further demonstrated that this model performed better than previously validated models for CMML [23, 25, 26].

Groupe Francais des Myelodysplasies Score

The French Cooperative MDS Group (GFM) published a model based on data from 312 CMML patients [10]. The GFM score incorporated Hgb < 10 g/dL and Plts < 100^9/L, but used total WBCs > 15×10^9 rather than the monocyte subset and added age > 65 years as prognostic variables. The investigators additionally evaluated the prognostic value of 18 commonly mutated genes. Unlike the Mayo data, *ASXL1* proved to be a significant predictor of OS and was added to the model. The resultant model included these five predictive variables and stratified patients into three risk groups: low risk with OS not reached, intermediate risk with median OS of 38.5 months, and high risk with median OS of 14.4 months.

Mayo Molecular Model

Given the discrepancy between the prognostic value of *ASXL1* mutations in the Mayo and GFM models, the two groups collaborated to analyze an expanded cohort of 466 CMML patients. *ASXL1* nonsense/frameshift mutations proved to be a risk factor for decreased OS, though not for leukemic transformation [16]. The authors incorporated this variable into the original Mayo Prognostic Model to create a refined score called the "Mayo Molecular Model" with four risk categories: low (0 risk factors), intermediate-1 (1 risk factor), intermediate-2 (2 risk factors), and high (≥ 3 risk factors) with median OS of 97 months, 59 months, 31 months, and 16 months respectively. This model can be useful to address the molecular data in patient discussions so that the ramifications of this testing can be demonstrated (in limited fashion) to them.

CPSS and CPSS-mol

Citing the prognostic impact of cytogenetic abnormalities in MDS, the Spanish group of MDS (GESMD) sought to identify prognostically significant cytogenetic abnormalities in CMML [26]. In a cohort of 414 CMML patients, the investigators identified low-risk abnormalities (normal karyotype, loss of Y chromosome) and high-risk abnormalities (trisomy 8, abnormalities of chromosome 7, complex karyotype). All others were considered intermediate risk. High-risk cytogenetics were associated both with decreased OS and increased risk for AML transformation. The GESMD then incorporated these cytogenetic factors with high-risk clinical factors

Table 2 CMML specific prognostic models developed between 2013 and 2018

CMML prognostic model	Year	Included variables	Risk categories	Median OS (months)
Mayo[29]	2013	Hgb < 10 g/dL, AMC > 10×10^9/L,	Low	32
		Plts < 100×10^9/L, IMC > 0%	Intermediate	18.4
			High	10
GFM Score[10]	2013	Age > 65, WBC > 15×10^9/L, Plts < 100×10^9/L	Low	Not reached
		Hgb < 10 g/dL (female) or Hgb < 11 g/dL (male),	Intermediate	38.5
		ASXL1 mutation	High	14.4
CPSS[30]	2013	Myeloproliferative type, CMML-2, WBC > 20×10^9/L,	Low	72
		Transfusion dependent, CMML cytogenetics	Intermediate-1	31
			Intermediate-2	13
			High	5
Molecular Mayo[16]	2014	Hgb < 10 g/dL, AMC > 10×10^9/L,	Low	97
		Plts < 100×10^9/L, IMC > 0%	Intermediate-1	59
		ASXL1 mutation (frameshift, nonsense)	Intermediate-2	31
			High	16
CPSS-mol[32]	2016	Myeloproliferative type, CMML-2, WBC > 20×10^9/L,	Low	Not reached
		Transfusion dependent, CMML cytogenetics	Intermediate-1	64
		ASXL1, NRAS, RUNX1, SETBP1 mutations	Intermediate-2	37
			High	18

(CMML-2, red blood cell transfusion dependence, and myeloproliferative subtype) to develop a new risk model called the CMML-specific prognostic scoring system (CPSS) [30]. The CPSS stratified patients into low (median OS = 72 months), intermediate-1 (median OS = 31 months), intermediate-2 (median OS = 13 months), and high (median OS = 5 months) risk categories. These categories also successfully stratified risk of 25% probability of leukemic transformation of 95 months, 40 months, 11 months, and 4 months, respectively.

In 2016, the CPSS was updated to include somatic mutations [31•]. The GESMD investigators found that 93% of patients in their cohort possessed a somatic mutation, with RUNX1, NRAS, SETBP1, and *ASXL1* all predicting inferior OS. The CPSS-mol, thus, included these somatic mutations and improved accuracy compared with the original CPSS.

Standard Treatments

Therapeutic options for CMML are limited and the treatment paradigms are largely borrowed from MDS and other MPNs. Indeed, much of the existing data for CMML therapy comes from high-risk MDS trials that included CMML [32, 33]. In result, the generalizability of these results to CMML can be a challenge. Studies designed specifically for CMML are increasing in frequency, which will better refine standard treatment paradigms and are more appealing to patients when the title of their trial contains the disease name they have been given.

The only therapy that has the potential to alter the natural history of CMML is allogeneic (allo) blood or marrow transplantation (BMT) [34–37]. Other available treatments are intended for palliation of symptoms or to decrease disease burden and possibly as a bridge to allo BMT. Risk stratification is critical as the treatment approach should be tailored to the aggressiveness of the disease. Patients with lower risk, asymptomatic disease may be monitored without initiation of therapy. The expectation management portion of this watchful waiting approach can be a challenge but incorporation of the aforementioned prognostic scores can help the clinical discussions. Though no strict indications exist, initiation of therapy should be considered for disease progression or onset of symptoms such as fever, weight loss, splenomegaly, hyperleukocytosis, leukostasis, increasing blasts, and severe cytopenias [38, 39]. Generally, CMML patients should be referred for clinical trials as standard options are limited in both efficacy and supporting data [40•, 41•, 42•].

When initiated, treatment should be tailored to the indication for treatment. Supportive measures such as erythropoiesis-stimulating agents (ESAs) and transfusions may be used in low-risk patients with cytopenias. Vigilance should be maintained in case paradigms of this nature stimulate expansion of existing splenomegaly. In patients with myeloproliferative symptoms related to leukocytosis or splenomegaly, initiation of cytoreductive therapy such as hydroxyurea or etoposide may elicit responses in approximately 60%

of patients [41]. AML-type induction chemotherapy may be considered in the case of leukemic transformation with plans to proceed to allo BMT [39]. Responses may be evaluated using recently proposed criteria by the MDS/MPN International Working Group [40•].

Hypomethylating Agents

In CMML patients with high-risk features based on prognostic scores or failure of conservative therapy, hypomethylating agents (HMAs) are usually the first line standard pharmacologic therapy. Various trials have demonstrated overall response rates (ORR) ranging from 30 to 75%, with many patients achieving complete remissions (CR) and resultant median OS of approximately 2 years [33, 43–47]. Recently, an Italian phase II trial evaluated 42 patients with high-risk CMML based on IPSS score treated with decitabine 20 mg/m^2 daily for days 1–5 of a 28-day cycle [42•]. The overall response rate was 47.6% and the median OS was 17 months. In patients who responded, the OS was significantly prolonged compared with those who did not respond to therapy. Treatment was well tolerated with moderate cytopenias being the most commonly encountered adverse event.

Many recent studies have attempted to identify patients most likely to benefit from HMAs. In a phase II study of 39 higher-risk CMML patients, lower expression of CJUN and CMYB genes predicted improved survival among patients on decitabine, though other somatic mutations had no significant effect [43]. In a cohort of 76 CMML patients treated with azacitidine, the presence of splenomegaly or marrow blasts > 10% portended worse OS [45]. In that trial, the investigators attempted to identify genetic lesions predictive of response to azacitidine, though none were significant. Finally, a retrospective study of 31 patients suggested that baseline AMC < 10 × 10^9/L and PB blasts < 5% were associated with improved OS in patients treated with azacitidine [48].

In MDS, HMA therapy has been prospectively shown to improve OS [46]. In contrast, no trial has demonstrated an OS benefit with HMA therapy when compared to supportive care in CMML. In a matched-pair analysis of 48 patients treated with azacitidine, there was no significant improvement in OS compared with either supportive care or hydroxyurea [49]. Similarly, a retrospective study using serial sequencing analysis showed that HMA therapy is not effective at reducing mutational burden nor delaying leukemic transformation, even in patients responding to therapy [50]. In total, these findings suggest that HMA therapy may not alter the natural course of CMML.

A novel HMA, guadecitabine, is currently being evaluated in phase III clinical trial (NCT02907359). In phase II studies of patients with MDS or CMML, ORR was 61%, CR rate was 28%, and median OS was 15.2 months [51]. ASTX727, a combination of oral decitabine with the cytidine deaminase inhibitor cedazuridine, has demonstrated an acceptable safety profile and is currently being compared to standard decitabine in a phase III trial (NCT03306264) [52]. It is less likely that newer preparations of HMAs will show any significant difference in the response rates over approved HMAs but alternative modes of administration may make the therapeutic option more palatable to patients.

Allogeneic BMT

The only curative therapy for CMML is allo BMT, though this therapy is marred by high risk of morbidity and mortality. Data supporting allo BMT is limited mostly to retrospective studies. Historically, these studies used myeloablative conditioning, which is highly toxic, yielding non-relapse mortality (NRM) as high as 50% and cure rates of 20–40% [36, 37]. Notably, most patients with CMML are not eligible for myeloablative HCT due to age and comorbidities. Thus, more recent studies have focused on reduced intensity conditioning (RIC) regimens. One study of 18 CMML patients treated with RIC allo BMT resulted in a 3-year OS of 31%, but with NRM of 31%, and a relapse rate of 47% [34]. A larger multicenter European study recently evaluated RIC allo BMT outcomes in 251 CMML patients and 422 MPN patients after progression to AML [35•]. For the CMML cohort, the 3-year OS was 36%, disease-free survival (DFS) was 30%, and NRM was 37% [35•].

Given the high risk and varying success of allo BMT for CMML, identifying patients most likely to benefit from the procedure has been a primary focus of recent studies. In an analysis of 513 patients reported to the European Group of Blood and Marrow Transplantation, relapse-free survival was 27% and OS was 33% at 4th year [53]. By multivariate analysis, complete remission prior to transplant was the only factor predictive of improved survival after transplant. Another European registry study correlated splenomegaly with reduced DFS and OS [54]. Additionally, high-risk cytogenetics, splenomegaly, comorbidities, MD Anderson Prognostic score, and CPSS have all been shown to correlate with worse outcomes after transplant [55, 56]. Though no study has confirmed a survival benefit with intensified conditioning, pre-transplant HMA therapy and the use of peripheral blood stem cell grafts are modifiable factors that have been associated with improved post-transplant DFS and OS, respectively [56, 57].

Novel Therapies

Given the limited treatment options and poor prognosis associated with CMML, novel therapies are desperately needed. A number of ongoing studies are evaluating such therapies for CMML, often in combination with HMA backbone.

Lenalidomide

Lenalidomide is a thalidomide analogue with efficacy in MDS, particularly in the setting of chromosome 5q deletion [58]. The North American Intergroup Study S1117 (NCT01522976) is a phase II/III multicenter trial that randomly assigned patients with high-risk MDS or CMML to azacitidine, azacitidine+lenalidomide, or azacitidine+vorinostat. Results of the phase II portion have been published [59•]. Azacitidine+lenalidomide resulted in no increase in serious adverse events compared with monotherapy. A subgroup analysis of the 53 CMML patients in the trial showed a significant improvement in ORR with azacitidine+lenalidomide versus azacitidine alone (68% versus 28%, $p = 0.02$), though no OS benefit was yet apparent. This clinical benefit was not demonstrated in the classical MDS patients. Azacitidine+vorinostat was not effective in the CMML group with only 12% ORR and toxicity was increased as well. The phase III portion is ongoing with the potential to modify standard practice in higher risk CMML.

Ruxolitinib

Janus kinase 2 (JAK2) mutations are commonly implicated as driver mutations in MPNs, particularly with a proliferative phenotype [60]. Ruxolitinib is a *JAK1/2* inhibitor that is approved for treatment of MPNs based on phase III data demonstrating improved DFS and symptom control [61, 62]. Notably, responses were seen even in the absence of a detectable *JAK2* mutation. Thus, a phase I trial evaluated ruxolitinib as monotherapy in 20 CMML-1 patients either as first-line therapy or after HMA failure [63]. No dose-limiting toxicities were observed. Though the trial was not designed to evaluate response, objective responses (spleen reduction, symptom improvement, and hematologic improvement) were observed in seven patients (35%). A phase II trial evaluating the efficacy of ruxolitinib in CMML is anticipated (NCT03722407).

Sotatercept

A novel agent under investigation is luspatercept, an activin type IIB receptor fusion protein that promotes release of mature erythrocytes into circulation [64]. It has demonstrated significant hemoglobin responses in MDS patients in a recent phase III trial as well as in patients with beta thalassemia [64]. Drugs with similar mechanism of action are appealing in CMML. Though CMML patients were not included in the luspatercept trial, sotatercept, an activating type IIA receptor fusion protein, has demonstrated efficacy in CMML [65, 66]. A phase II, dose-finding study evaluated this drug in patients with anemia due to low-risk MDS or CMML after failure with ESAs [66]. With 74 patients treated, grade 3–4 treatment-related adverse events (lipase increase, anemia) were observed in 5% which makes it particularly appealing as another alternative to augment hemoglobin levels. Hematologic improvement was observed in 49% of patients on the trial.

Tipifarnib

Farnesyltransferase (FT) is an enzyme required for post-translational attachment of farnesyl group needed for intracellular signaling and appears to be more effective in the absence of RAS pathway mutations [67]. As RAS pathway mutations are implicated in ~30% of CMML cases, an inhibitor of FT called tipifarnib is currently being evaluated in phase II clinical trial of CMML patients, many of whom relapsed after HMA failure (NCT02807272) [17]. Interim safety analysis from that trial showed that thrombocytopenia, neutropenia, diarrhea, and nausea/vomiting are the most common adverse events [67]. Of seven patients evaluable for response, two had objective responses, four had stable disease, and one had progressive disease. Additionally, investigations are forthcoming.

Other Emerging Therapies

A number of other emerging agents for CMML are in earlier stages of development. Pacritinib, a *JAK2* inhibitor, may be an effective alternative to ruxolitinib with a more favorable side effect profile based on studies in myelofibrosis [68]. H3B-8800 is a modulator of *SF3B1* (NCT02841540) that has shown efficacy in xenograft models carrying spliceosome mutations [69]. Lenzilumab, a humanized monoclonal antibody that targets colony stimulating factor 2 and granulocyte macrophage colony stimulating factor, is currently being investigated (NCT02546284) based on preclinical data demonstrating inhibited growth of CMML cells [70]. The sonic hedgehog inhibitor glasdegib has demonstrated reduction of leukemic stem cells and, thus, is being studied in CMML and other myeloid malignancies (NCT02367456) [71]. Finally, as CD123 is expressed in CMML, the CD123 antibody SL-401 is being studied in an ongoing phase 2 trial (NCT02268253) [72].

Our Approach

The diagnostic workup of CMML should now include somatic mutation panels to assist with diagnosis and prognosis. Treatment strategies should be adjusted to account for the aggressiveness of disease (by CPSS-mol or Mayo molecular models). For low-risk disease, monitoring or symptom management may be appropriate. For higher risk, fit patients, the goal of therapy should be discussed, including the potential for curative paradigm with an allo BMT. Consultation with centers seeing higher volumes of CMML patients is often prudent early in the disease course.

When medical therapy is discussed, both standardly available, as well as investigational therapies should be considered. Since standard therapies have limited efficacy, we do recommend clinical trials when available and appropriate. This does, however, require attention to the constellation of clinical symptoms and biologic data in an individual patient to optimize benefit and minimize toxicity. For example, in a patient with fatigue from mild anemia and no splenomegaly, therapies aimed at hemoglobin augmentation should be prioritized over a therapy which might cause marked cytopenias and predispose to infection when the patient at baseline has a preserved neutrophils.

Recent consensus guidelines recommend that CMML patients with a CPSS score of Intermediate-2 or higher should be managed with curative intent [73]. Still, the evaluation should be individualized based on the patient's age, comorbidities, and a shared decision-making approach. Based on the patient's values and unique circumstances, transplantation may be appropriate for CPSS lower risk patients, such as those with high-risk cytogenetics, increased blasts, or high transfusion needs. Because of these subtleties, it is appropriate for any patient with a diagnosis of CMML to be referred to a transplant center for evaluation.

The optimal pre-transplant therapy has not been rigorously determined. Extrapolating from other myeloid diseases, transplant outcomes are inferior in the setting of progressive disease or elevated blasts [74–76]. In select cases with stable, low disease burden and a readily available donor, immediate transplant could be appropriate. This strategy does pose a risk, however, of disease progression while completing the pre-transplant evaluation or transplant-related mortality when the disease is affecting the patient less in the short term. Alternatively, disease control with an HMA, chemotherapy, or a clinical trial should be considered prior to transplant. Often, HMA therapy as a bridge to transplant is the recommended standard. However, as HMAs may require 4–6 cycles to take effect, induction chemotherapy is preferred in the setting of rapidly progressing disease or transformation to AML. Ultimately, the goal should be to have at least stable disease and a bone marrow blast percentage of less than 10% at the time of transplant. After meeting these metrics, transplant should proceed efficiently. The medical team should be cautious of delaying transplant in hopes of reaching a deeper remission as this risks' loss of an already adequate response and, thus, may preclude the opportunity for a potential path to cure.

Conclusions

CMML remains a difficult myeloid malignancy with variable prognosis and few treatment options. Significant recent advances have helped more accurately predict prognosis in CMML patients. Recognition of the importance of somatic mutations has helped refine prognostic scores. *ASXL1* mutations, in particular, have consistently correlated with worse outcomes. Despite these advances, it is unclear which prognostic model is most accurate as, in individual patients, they may differ in their predictions. Future studies should continue to refine prognostic accuracy as therapeutic decisions are dependent on the aggressiveness of the disease.

Generally, treatment options for CMML follow paradigms similar to MDS and/or MPNs. However, therapies are typically not as effective in CMML as they are in these other conditions. Low-risk CMML patients may require only observation or supportive therapies (e.g., transfusions, ESAs). For higher risk CMML patients, HMAs remain the cornerstone of medical therapy. A number of novel therapies have shown promising preliminary results both in combination with first-line HMAs or to treat patients in the relapsed setting. However, no medical therapy has proven effective in altering the natural course or improving survival in CMML. Thus, when available, an interventional clinical trial is almost always the preferred treatment strategy. In general, all fit CMML patients should be evaluated for allogeneic BMT. The decision to transplant should include careful consideration of prognostic models, patient fitness, and factors that predict post-BMT outcomes.

Overall, recent advances have improved our understanding and treatment of CMML. Future studies that are specific to CMML, in contrast to MDS studies that include CMML, will help to further optimize management approaches.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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