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Chronic myelomonocytic leukemia: Forefront of the field in 2015

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Abstract

Chronic myelomonocytic leukemia (CMML) includes components of both myelodysplastic syndrome and myeloproliferative neoplasms and is associated with a characteristic peripheral monocytosis. CMML is caused by the proliferation of an abnormal hematopoietic stem cell clone and may be influenced by microenvironmental changes. The disease is rare and has undergone revisions in its classification. We review the recent classification strategies as well as diagnostic criteria, focusing on CMML's genetic alterations and unique pathophysiology. We also discuss the latest molecular characterization of the disease, including how molecular factors affect current prognostic models. Finally, we focus on available treatment strategies, with a special emphasis on experimental and forthcoming therapies.

Keywords

chronic myelomonocytic leukemia; myelodysplastic syndrome; myeloproliferative neoplasms

1. Introduction

Chronic myelomonocytic leukemia (CMML) is generally recognized as a chronic leukemia with persistent monocytosis and components of both myeloproliferative neoplasms and myelodysplastic syndrome [1]. It has been recognized as a distinct disease for more than 40 years, although until 2002 it was grouped with myelodysplastic syndrome (MDS). In 1971, Saarni and Linman recognized qualitative abnormalities in more than one lineage in patients with monocytoid leukemic transformation; 36% of their patient series had peripheral

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monocytosis, and 31% demonstrated a preleukemic phase, sometimes for as long as 9 years [2, 3]. The term *myelomonocytic leukemia* denotes both the myeloid and the monocytoid features of the disease. In 1972, Zittoun et al. described 27 cases of subacute myelomonocytic leukemia [4, 5]. The first significant-size cohort of patients to be recognized as having CMML was described in 1975 and included 18 elderly patients with unexplained monocytosis, cytopenias, and splenomegaly [6, 7]. Five of the patients survived longer than 5 years. This finding indicated that intensive chemotherapy may not be needed in this patient population and led to recognition of CMML as a distinct entity by the French-American-British (FAB) Group in 1976 [8]. Since then, several groups have categorized the clinical manifestations and outcome of CMML as a subset of MDS. However, some patients with CMML may express features of myeloproliferative neoplasms (MPN; also known as myeloproliferative disorders or MPD) at the time of diagnosis or at another stage in the course of the disease. Consequently, CMML has remained under-researched and is often excluded from MDS and MPN clinical trials.

Here we discuss the classification and diagnosis of CMML, the clinical features and epidemiology of the disease, and current insights into its pathophysiology. We review established treatments for patients with CMML as well as state-of-the-art approaches.

2. Classification and diagnosis

2.1. FAB and WHO classifications

From the time CMML was first identified 50 years ago, debate has continued on its proper place in the classification of hematologic malignancies. In 1982, the FAB Group classified CMML as part of MDS, given the morphologic evidence of dysplastic hematopoiesis [9], but whether CMML should be classified as myeloproliferative or myelodysplastic remained unclear. Recognizing the heterogeneity of the clinical features of the disease, the FAB Group later proposed a reclassification of patients into two subtypes based on white blood cell (WBC) count at diagnosis [10]. The FAB classification is shown in Table 1. Patients with WBC counts of $\leq 13 \times 10^9$/L were considered to have myelodysplastic CMML (MD-CMML), and those with WBC counts of $>13 \times 10^9$/L were considered to have myeloproliferative CMML (MP-CMML). The separation of patients by this classification system remains problematic because the two groups have overlapping features. However, since many studies have classified CMML according to FAB criteria, the differences between MD-CMML and MP-CMML are important to interpreting the studies' findings.

Nosslinger et al. conducted a retrospective analysis of 91 patients with CMML who had been treated primarily with supportive care [11]. At the time of diagnosis, patients with MPCMML (n, 31; 34%) had higher lactate dehydrogenase (LDH) levels, absolute neutrophil counts, and bone marrow cellularity values than did patients with MD-CMML (n, 60; 66%). The median overall survival (OS) duration for the MP-CMML group (16 months) was significantly shorter than that for the MD-CMML group (31 months) (p-value, 0.03), with a higher risk of leukemia transformation in the MP-CMML group, indicating differences in outcomes between the two groups. Onida et al. retrospectively analyzed 213 patients with CMML treated with various approaches, including chemotherapy, and classified each patient's CMML as MD-CMML (n, 74; 35%) or MP-CMML (n, 139; 65%) on the basis of

the patients' WBC counts [12]. Although the OS rates were similar in the first few months of treatment, a significant difference appeared after 16 months, with a higher OS rate for MD-CMML patients. The difference in rate of leukemic transformation, however, was not statistically significant [12]. Voglova et al. analyzed 69 patients with CMML, 31 (45%) classified as MD-CMML and 38 (55%) as MP-CMML [13]. Cytogenetic abnormalities were more frequent among patients with MP-CMML. The median OS was significantly longer in the MD-CMML group than in the MP-CMML group (30 vs. 16 months, respectively; p-value < 0.01), and there was no significant difference in leukemic transformation. However, in 24 patients with MD-CMML, the WBC count increased to more than 13×10^9/L over the course of the disease. The authors concluded that using the WBC count obtained at diagnosis as the single criterion for subclassification of CMML did not seem fully justified and that MD-CMML and MP-CMML should be considered different stages of the same disease, rather than two different diseases [13].

In an effort to resolve this discrepancy, and to eliminate the arbitrary use of WBC counts to classify patients with CMML, the World Health Organization (WHO) in 2002 recognized CMML as a distinct entity for the first time and moved it to a new category called MDS/MPD [3]. This category also included atypical chronic myeloid leukemia and juvenile myelomonocytic leukemia. The FAB and WHO diagnostic criteria for CMML are compared in Table 1. The FAB system includes both MD-CMML and MP-CMML and is based on the WBC count, while the WHO classification differentiates CMML-1 and CMML-2 and is based on blast percentages. The quantification of blast percentages for peripheral blood and bone marrow include myeloblasts, monoblasts, and promonocytes [3]. Most recently, Schuler et al. proposed classifying patients with less than 5% medullary blasts as CMML-0, and sub-classifying each group of patients based on dysplasia vs. proliferation, as these groups have distinct clinical outcomes [14].

2.2. Diagnostic considerations

2.2.1. Peripheral blood counts—Monocytosis in the bone marrow or peripheral blood represents a major diagnostic criterion for CMML. However, in some cases, eosinophilia may present as a part of the CMML disease process. Because monocytosis and/or eosinophilia are cardinal features of several other diseases, a thorough search for other monocytic diseases must be conducted and those diseases must be systematically ruled out when a new patient is evaluated for possible CMML. In addition, a proper evaluation for infections and chronic inflammatory states as well as other malignancies known to cause monocytosis or eosinophilia should be conducted before CMML is diagnosed [15].

2.2.2. Cytogenetic analysis—There is no pathognomonic cytogenetic abnormality in CMML [15, 16]. Previously, some cases of CMML were associated with translocation of chromosomes 5 and 12 [t(5;12)(q33;p13)] [17-20], which is associated with expression of a fusion transcript that links the ETS-variant gene *TEL* with *PDGFRB* [21]. These patients are best classified as "myeloid neoplasia with *PDGFRB* rearrangements" even if they have features of CMML.

Other chromosomal abnormalities have been described in patients with CMML, including t(3;6)(q12;24), t(5;7)(q33;q11.2), der(9)t(1;9)(q11;q34), der(14)t(1;14)(q12;p11), and t(11;19)(q23;p13.1) [22-27]. One study also identified translocations involving the RET oncogene, specifically t(10;22)(q11;q11) and t(6;10)(q27;q11), as responsible for two separate cases of CMML [28]. First, a large study using data from the Spanish Registry of Myelodysplastic Syndromes found abnormal cytogenetic profiles in 110 (27%) of 414 CMML patients [29]. Two subsequent and recent studies found abnormal karyotype in 30% and 28% of 417 and 409 CMML patients respectively, confirming that overall ~30% of CMML patients have an abnormal karyotype, while ~70% have normal karyotype [30, 31].

Single nucleotide polymorphism arrays (SNP-A) have been employed to study chromosomal lesions in patients with CMML [32, 33]. Uniparental disomy (UPD), which results from segmental DNA recombination during mitosis, was a common event in MDS/MPN (35%), especially in CMML patients tested (n = 24) [32]. In a comprehensive follow up study that included 54 CMML patients (36 CMML-1 and 18 CMML-2 patients), SNP-A again detected widespread acquired copy-neutral loss of heterozygosity (a result of UPD) [33]. Given the predominance of UPD in CMML, detection of these chromosomal abnormalities has been critical in identifying genes such as *CBL* and *TET2* that are important in CMML pathogenesis [33-36].

2.2.3. Molecular phenotyping—More recently, key molecular tests have been identified that aid in the workup of patients with suspected CMML. Importantly, *PDGFRB* rearrangement at chromosome band 5q33 is present in some CMML patients and is associated with eosinophilia [16]. These patients may respond to tyrosine kinase inhibition (with imatinib mesylate therapy); therefore, knowledge about this genetic aberration can be critical to treatment (see section 5 below) [37, 38]. Though *JAK2* V617F mutations are less frequent in CMML than in polycythemia vera, essential thrombocytosis, or primary myelofibrosis [39-42], in one series, Pich et al. found that 8 (10.2%) of 78 patients with CMML were positive for the *JAK2* V617 mutation at diagnosis [43]. JAK2 inhibitors have been characterized as potentially useful for treatment of CMML, and limited numbers of patients have been treated with them (see section 5 below) [44, 45].

Both KRAS and NRAS mutations, important in multiple hematologic malignancies, have been implicated in approximately 30%-40% of patients with CMML [46-48]. Other common molecular abnormalities (with percentages of CMML patients in parentheses) include mutated *TET2* (~30-60%), *ASXL1* (~40%), *SRSF2* (~45%), *RUNX1* (~15%), *CBL* (~10%), *IDH1/2* (~5-10%), *U2AF35* (9%), *ZRSF2* (8%), *UTX* (8%), *DNMT3A* (~2-10%), *SF3B1* (6%), *U2AF1* (5%), *FLT3* (~3-4%), *EZH2* (~5%), and *SETBP1* (~4-5%) [49-58]. These genes are associated with epigenetic regulation, mRNA splicing, embryonic development, protein ubiquitination, and cellular proliferation. Several of these genes identified are involved in spliceosome function, and may be mutually exclusive [56]. The biological significance of these mutations is related to the clonal architecture of the disease (see subsection 3.2 below), and some of the mutations may be used as prognostic indicators (see subsection 4.1 below). Interestingly, *ASXL1* and *SF3B1* mutations tended to occur with an abnormal karyotype (p-values 0.04 and 0.03 respectively), while *SRSF2* mutations more frequently occurred with a normal karyotype (p-value = 0.02) [31].

2.3. Epidemiology and presentation

CMML is rarely diagnosed in younger adults, with the median age at diagnosis being about 70 years, similar to the median age of patients at diagnosis for MDS [5, 59]. The clinical presentations are protean and can represent the full spectrum of both MDS and MPN [60]. Common presentations include signs and symptoms of bone marrow suppression (anemia, thrombocytopenia, neutropenia), leukocytosis, lymphadenopathy, and hepatosplenomegaly [15, 60]. Furthermore, some reports have described leukemia cutis as the initial manifestation of CMML or heralding transformation to acute myeloid leukemia (AML) [61]. In most reports, patients with MP-CMML were older than patients with MD-CMML, but the differences were not statistically significant [7, 11]. Furthermore, male predominance was observed more frequently in patients with MD-CMML than in those with MP-CMML, but again the differences were not significant [7, 11].

3. Biology and pathophysiology

The pathophysiology of CMML is still not fully understood, in large part because CMML has been frequently studied as a subtype of MDS rather than as a separate entity. The high variability of the clinical presentation and the course of the disease reflect the heterogeneity of CMML's pathogenetic features. Multiple theories about the biology of CMML, based on cellular, cytogenetic, and molecular abnormalities and supported by animal models, were developed over the past two decades, and recently a number of models to investigate the pathogenesis of CMML have emerged.

3.1 Cellular biology

Decreased apoptosis as an alternative pathway to tumorigenesis has been proposed in the pathogenesis of MDS as well as CMML. A competitive reconstitution assay demonstrated that long-term repopulating cells deficient in *Bid*, a BH3-only proapoptotic protein, gave rise to expanded myelomonocytic cells *in vivo* [62]. A mouse model recapitulating this phenomenon is discussed below in subsection 3.2. In support of the idea that decreased cellular apoptosis is a manifest contributor to CMML, Boudad et al. reported increased expression of antiapoptotic proteins Bcl-2 and Bcl-xL in patients with CMML [63]. In another study, increased expression of the cell cycle gene *CCND1* (encoding cyclin D1) was also demonstrated in CMML patients compared with other FAB subgroups of MDS [64]. These findings suggest that the combination of specific decreased-apoptosis pathways and critical cell cycle pathway dysregulation directly contributes to the pathogenesis of CMML.

Recent investigation into immune checkpoint tolerance genes in myeloid malignancies revealed that CMML has increased expression of PD-L1 compared to AML [65]. Treatment with hypomethylating agents increased expression of PD-L1 and other related immune checkpoint genes in patients [65]. The work suggests that therapies blocking immune checkpoints, especially in conjunction with hypomethylating agents, may be an option for patients with CMML.

Angiogenesis has been shown to play a pivotal role in human leukemia. Pruneri et al. reported significant increases in microvascular density (MVD) in patients with CMML and

MDS [66]. Aguayo et al. demonstrated that plasma levels of vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) were elevated in patients with CMML compared with the levels in non-leukemic control patients and patients with other leukemias including MDS [67]. Likewise, Wimazal, et al. found increased MVD and elevated levels of VEGF in the bone marrows of patients with CMML; immature myeloid cells were the source of VEGF [68]. Alexandrakis et al. further confirmed the importance of angiogenesis in CMML by demonstrating increased MVD and increased levels of angiogenin and interleukin 6 in patients with CMML [69, 70]. Finally, Bellamy, et al. proposed an autocrine function of VEGF, demonstrating that some patients' CMML cells expressed cytoplasmic VEGF as well as the membranous VEGF receptors Flt-1 and KDR. Inhibiting VEGF prevented CMML colony growth *in vitro* [71]. In total, these studies strongly suggest that microenvironmental influences, particularly angiogenesis, play a special role in the development and maintenance of CMML.

3.2 Molecular underpinnings

At the molecular level, CMML shares some characteristics with other myeloproliferative neoplasms. Activation of the JAK/STAT pathway has been the prominent molecular feature of polycythemia vera and is also a feature of primary myelofibrosis and essential thrombocythemia [72, 73]. Mutations in the JAK2 gene are less common in CMML [39, 74, 75], however GM-CSF dependent STAT5 hypersensitivity has been noted in some CMML patients [76]. These studies suggest reliance on GM-CSF and the JAK/STAT pathway, and the potential for therapeutic intervention with anti-GM-CSF or JAK2 inhibition, even in the absence of mutated JAK2 [76].

Other molecular and genetic markers have been sought in CMML. Among hematologic malignancies, CMML is associated with the highest incidence of RAS pathway mutations [74]. MacKenzie et al. have shown that irradiated mice that undergo transplantation with *Nras*-mutated bone marrow cells develop myeloproliferative-like disease. Along with RAS pathway mutated mouse models described below in section 3.3, this work supports the theory that the RAS activation is a significant contributor to myeloproliferation in CMML [77].

Driver mutations responsible for the development of CMML have been studied by analyzing mutational data generated to date. Using single-cell-derived colonies from 28 patients with CMML, Itzykson et al. were able to determine that early mutations in *TET2* were likely responsible for development of a dominant granulomonocytic clone [78]. After the acquisition of additional mutations, in spliceosome and epigenetic factors, for instance, the proliferative advantage and abnormal differentiation of a hematopoietic stem/progenitor cell emerges, as does the clinical entity CMML [79]. The findings suggest that a clonal hierarchy might be identified so that treatments would specifically target abnormal stem cell clones, to allow normal stem cells to proliferate and differentiate appropriately [79]. TET2 is recognized as an especially important player in the development of CMML [80]. Disruption of *TET2* was demonstrated to act on the hematopoietic system at the level of the stem cell, promoting self-renewal, increasing 5-hydroxymethylcytosine, preventing normal differentiation, and resulting in skewing towards myeloid/monocyte development [81-84].

Other genes found mutated in CMML have also been shown to promote myeloid differentiation through methylation effects on the hematopoietic stem cell. ASXL1 was determined to act through the loss of H3K27 methylation by polycomb repressive complex 2, and loss of *ASXL1* promoted myeloid differentiation in a proliferative setting [85]. In support of the idea of driver mutations in the stem cell compartment, Cilloni et al. also reported abnormal activation of the tyrosine kinase ROS1 in the stem-like cell population of 70% of CMML patients, and this abnormal activation may drive oncogenicity [86].

3.3 Mouse models

Several mouse models have capitalized on findings from cellular and molecular studies, and recapitulated elements of CMML. A number of mouse models that overexpress Nras or Kras in the hematopoietic compartment have been shown to develop CMML-like disease [87-89]. One model has recently been used to show effectiveness of combined ERK/MEK inhibition in for treatment of the Nras-driven murine CMML mimic [90].

Mice that were deficient in Bid proapoptotic protein developed a myeloid leukemia that clinically and morphologically resembled adult CMML [62]. Additionally, enforcing production of Bcl-2 protein under the control of the human myeloid related protein 8 (hMRP8) promoter, induces proliferation of myelomonocytic cells, and has been proposed as a leukemic stem cell model for CMML [91, 92]. These model supports the idea that decreased apoptosis is a fundamental mechanism in the development of CMML.

Tet2 deficient mice were predisposed to develop a myeloproliferation and a CMML-like malignancy, and mice transplanted with *Tet2* deleted hematopoietic cells developed monocytosis and splenomegaly [82, 84]. Asxl1 deficient mice have also recently been shown to develop myelodysplasia/CMML [93, 94]. In these models, *Asxl1* haploinsufficiency led to a milder myeloproliferation, and combined *Asxl1*/*Tet2* knockout led to a more aggressive MDS [93, 94]. Interestingly, methylation effects of *Asxl1* knockout altered expression of apoptosis related genes such as *Bcl2*, suggesting this as a mechanism acting on hematopoietic stem cells leading to the observed phenotype [93]. Finally, hematopoietic-restricted deletion of the tumor suppressor *Bap1*, whose protein product is believed to cooperate with ASXL1 in epigenetic regulation, led to MDS and splenomegaly in mice [95].

Another model where mice developed CMML-like features was created with conditionally deleted TGF-β activated kinase 1 (Tak1) in the myeloid compartment [96]. Mice with myeloid-deficient Tak1 developed a myelomonocytic expansion, splenomegaly, and murine AML as they aged [96]. The deletion appeared to affect cytokine mediated signaling, and was associated with genomic instability [96]. In another recently developed mouse model, deletion of transcription intermediary factor 1γ (*Tif1g*) initiated age-dependent development of myeloproliferation reminiscent of CMML [97]. The gene was demonstrated to be an epigenetically regulated tumor suppressor gene [97].

Additional mouse models of MDS and MPN are especially promising in recapitulating clinical manifestations of CMML that are seen in patients, and may be helpful in elucidating the pathogenesis of CMML. PDGFRB mutant mice develop a disorder that is not unlike myeloproliferative CMML [38, 98, 99]. The over-production of the oncogenic portion of the

Hmga2 gene induces hematopoiesis in stem cell progenitors and produces a mouse model that mimics MPN [100]. Similarly, the deletion of the *Dido1* gene, when knocked out in a mouse model, produces a human-like MPN/MPD disease [101]. These mouse models may lead to additional understanding of myelomonocytosis at the level of cellular and molecular biology.

4. Prognosis

4.1. Prognostic scoring systems

One of the most important prognostic indicators in CMML is the blast count, which is the basis for differentiating CMML-1 and CMML-2 in the WHO classification. CMML-1 presents with <5% blasts in the blood and <10% blasts in the bone marrow and has an 18% chance of transformation to AML within 5 years. CMML-2 has 5-19% peripheral blood blasts and/or 10-19% bone marrow blasts and is associated with a 63% 5-year risk of progression to AML [102].

Several prognostic scoring systems used for patients with MDS have been employed for patients with CMML [12, 103-112]. All of those systems score patients on the basis of various critical hematologic, clinical, or biochemical indices such as complete blood counts, bone marrow biopsy characteristics, age, sex, splenomegaly, prior malignancies, antecedent hematologic disease, presence of *RAS* mutations, and levels of lactate dehydrogenase and β2-microglobulin. Some prognostic systems have specifically been proposed for patients with CMML [12, 51, 104, 110, 113, 114]. Most recently, Such et al. described the CMML-specific prognostic scoring system (CPSS), which relies on the WHO subclassification, the FAB subclassification, CMML-specific cytogenetic classification (low risk = normal and isolated −Y; intermediate risk = all other abnormalities not included in low or high risk; and high risk = trisomy 8, complex, and chromosome 7 abnormalities), and erythrocyte transfusion dependency [110]. Another recent and useful risk model, the Global MD Anderson Prognostic Scoring System (GMDAPS), was proposed for all MDS and CMML patients, regardless of specific disease type, prior therapy, or duration of disease. G-MDAPS is based on performance status, age, platelet count, hemoglobin value, percentage bone marrow blasts, white blood cell count, karyotype, and prior transfusion [111]. CPSS and G-MDAPS are summarized in Table 2. A refined MDAPS score, more specific for patients with CMML, was recently proposed [114]. It is also reported that therapy-related CMML carries a worse prognosis than *de novo* CMML [115].

4.2. Impact of cytogenetic and molecular studies on prognosis

4.2.1. Cytogenetics and prognosis—In a study using data from the Spanish Registry of Myelodysplastic Syndromes, CMML patients with an abnormal karyotype (27%) had a higher leukemia transformation rate (26% vs. 12% at 2 years and 36% vs. 27% at 5 years; p-value, 0.01) and shorter OS (median 16 vs. 36 months, p-value < 0.01) [29]. Three independent risk groups were created on the basis of cytogenetic abnormalities: low risk (-Y, diploid/normal), high risk (trisomy 8, chromosome 7 abnormalities, complex cytogenetic abnormalities), and intermediate risk (all other abnormalities). In a multivariate analysis based on these risk groups, cytogenetic stratification was identified as an independent

prognostic factor for OS in patients with CMML [29]. This finding confirmed those of other studies showing the usefulness of cytogenetic risk stratification for prognosticating CMML outcomes [12, 109]. A subsequent confirmatory study determined that CMML patients who had abnormal karyotype (30%) had a higher rate of 2-year transformation to AML (29% vs. 14%, p <0.001), and shorter OS (median 19 vs. 33 months, p-value < 0.0001) [30]. Monosomal karyotype has been independently shown to confer worse prognosis in patients with CMML [116].

4.2.2. Molecular characterization and prognosis—Future prognostic scoring systems for CMML will likely use molecular analysis in combination with clinical and cytogenetic data. Mutational analysis is especially important considering that approximately 70% of CMML patients have normal diploid cytogenetics [29-31]. For example, *TET2* mutations may not offer prognostic information except for certain patients with CMML-1, and *SETBP1* mutations are associated with poor prognosis [53, 54, 117, 118]. *CBL* mutations in both CMML-1 and CMML-2 are associated with poorer outcomes, and *CBL* mutant patients tended to have splenomegaly [52]. Although *FLT3* mutations occur in approximately one-third of AML patients, they are far less common in CMML (~4%) and do not predict outcomes [57]. Among the spliceosome mutations in *SRSF2*, *SF3B1*, and *U2AF35* that have been identified in CMML (most commonly in *SRSF2*), none are prognostic for outcome [56, 58]. *RUNX1* mutations, on the other hand, are thought to predict transformation to AML [119]. Some recent prognostic models have begun to take into account mutational information, such as the mutational status of *ASXL1*, which may confer an adverse prognosis when mutated [51, 113, 120]. These models are promising and will need continued streamlining and validation. A challenge to creating a uniform model is the bias created by inclusion or exclusion of patients in studies at different institutions since CMML shares features with both MDS and MPN [113].

5. Treatment

Treatment for CMML has been investigated mainly as part of MDS clinical trials that included patients with the CMML subtype. In the past several years, interest into the use of newer agents for CMML has been growing. Traditionally, patients are started on treatment when they begin to experience disease-related complications such as cytopenias or immunosuppression leading to fever or infection, or significant hematologic abnormalities including worsening transfusion dependence and increasing blast percentage. There are no currently accepted standards for determining the optimal time to initiate therapy for a particular patient. Even as new therapies emerge, supportive care remains integral to the management of patients with CMML. Primary measures include symptom management such as blood product transfusions for anemia. Growth factor support with erythropoietin may be also used, since there is anecdotal evidence that it may be of benefit [121].

5.1. Stem cell transplantation

Currently, the only known curative treatment for CMML is allogeneic hematopoietic stem cell transplantation (HSCT) [122]. For younger patients with good performance status, HSCT may be preferred. However, because most patients with CMML are older than 70

years and are thus poor candidates for stem cell transplantation, alternative treatments have been sought. Recent evidence suggests that the number of additional comorbidities may relate directly to the success or failure of transplantation in CMML [123].

All studies investigating HSCT in CMML have been retrospective. The largest study of its kind used the European Blood and Bone Marrow Transplant (EBMT) database and included 283 patients. At the time of analysis, 38% of the patients were alive and free of disease. In total, 25% of patients experienced a relapse; however, the risk of relapse was lower in patients who experienced grade II-IV acute graft-versus-host disease (GVHD). Of interest, several factors were ruled out as prognostic indicators for relapse-free survival or OS in transplant patients, including CMML subtype, cytogenetic abnormalities, conditioning regimen, use of total body irradiation, stem cell source, T-cell depletion, type or grade of GVHD, age or disease status at transplantation, and HLA (human leukocyte antigen) type or sex of donor. The non-relapse mortality rate was 37% and was found to be lower in patients who had received peripheral blood stem cells or who had undergone transplantation after 2002 [124]. Relapse rates were comparable to those in other studies [123, 125-132]. One earlier study with 21 CMML patients found a disease-free survival rate of 43% with a median follow-up of 6-9 years [132]. In total, those studies showed high treatment-related mortality but suggested the strong possibility of long-term disease-free survival.

Several studies included patients with CMML who received reduced-intensity conditioning with a transplant [124-126, 129, 131]. It has been suggested that this approach is appropriate for patients with CMML who are advanced in age and/or have other significant comorbidities. Relapse-free survival rates for CMML patients receiving HSCT have improved in recent years [15, 122]. This is hypothesized to be the result of advancements in supportive care, reduced-intensity conditioning, and better HLA matching protocols [122]. The utility of treating CMML patients undergoing transplantation in the same manner as MDS transplant patients has yet to be prospectively studied [15].

Some patients received donor lymphocyte infusions (DLI) after transplantation. Of six patients with CMML who received DLI in two studies, two benefited from DLI, achieving long-term complete remission (CR). However, there is no consensus about which CMML patients might benefit from DLI, and the patients who did benefit also had significant chronic GVHD [127, 133].

5.2. Cytotoxic chemotherapy

Cytoreductive therapy has traditionally been used to control early-stage disease. Early attempts to control disease with hydroxyurea were more successful than etoposide, and consequently hydroxyurea is still commonly used [134]. For progressive disease, low-dose cytarabine, a nucleoside analog, has also been used. However, very few studies have looked at cytarabine specifically in CMML, and most included other types of MDS. In cases of transformation into AML, traditional high-dose cytarabine-based regimens that are used for *de novo* AML are utilized. Other investigational cytotoxic chemotherapies are discussed below.

5.3. Hypomethylating agents

Some recent studies focused on hypomethylating agents for CMML, and several of the studies investigated 5-azacytidine or decitabine [135-141]. Both compounds were approved for CMML by the U.S. Food and Drug Administration. In the European Union, subcutaneous 5-azacytidine was approved for CMML patients not eligible for transplantation who have 10%-29% bone marrow blasts and do not have an MPD. The use of hypomethylating agents is further supported by a recent mutational analysis of 52 patients with CMML demonstrating mutations in genes known to regulate methylation, including *TET2*, *UTX*, *EZH2*, and *DNMT3A* [52].

Three studies with 18, 19, and 31 CMML patients treated with decitabine found CR rates of 10%, 50%, and 58% and objective response or hematologic improvement rates of 67%, 11%, and 19%, respectively [135-137]. More recently, a study of 39 patients with advanced CMML treated with decitabine found CR in 10% of patients and an overall response rate of 38% (median duration of response 13 months, range 4 to 21 months) [139]. Similarly, a study of 38 CMML patients treated with 5-azacytidine found CR in 11% of patients and HI in 25% of patients (median duration 6.5 months, range 3 to >50 months) [140]. The most common adverse effects were those associated with cytopenias.

5.4. Investigational agents

Investigational agents that have been used for treatment of CMML include topoisomerase I inhibitors, sapacitabine, clofarabine, tyrosine kinase inhibitors, thalidomide/lenalidomide, all-trans retinoic acid, histone deacetylase inhibitors, JAK2 inhibitors, and farnesyltransferase inhibitors. Treatments of CMML with these agents largely reflect the approaches used for MDS, and they are outlined in Table 3.

The most studied topoisomerase 1 inhibitor is topotecan, which has been used alone, in combination with cytarabine, and in combination with thalidomide [142-146]. Treatment with single-agent topotecan produced a CR rate of 28% in 25 patients with CMML [142], and addition of cytarabine in a combination regimen increased the CR rate to 44% in another study, which included 27 patients with CMML [144].

Sapacitabine is an orally administered deoxycytidine analog whose mechanism of action is distinct from that of cytarabine [147]. In a single study at The University of Texas MD Anderson Cancer Center, two patients with CMML treated with sapacitabine responded with CR or bone marrow CR for 2 and 3.3 months, respectively. A patient whose CMML transformed into AML also responded to sapacitabine with CR without recovery of platelets for 2.2 months. All three patients had been treated previously with decitabine, and the AML patient had also been treated previously with clofarabine [148]. Clofarabine, a second-generation nucleoside analog has also been tested in patients with MDS including those with CMML. In another MD Anderson study, out of 6 patients with CMML, 2 achieved CR [149]. Both clofarabine and sapacitabine are currently used when disease progresses despite the use of hypomethylators [150].

Tyrosine kinase inhibitors have been used specifically to treat CMML associated with a rearrangement of the platelet-derived growth factor receptor beta (*PDGFRB*) gene, which is

a tyrosine kinase receptor in the MAP kinase pathway [37, 38]. Some CMML patients without a *PDGFRB* rearrangement who were treated with imatinib had no significant response [151, 152]. One study investigated the use of semaxanib, a multikinase inhibitor that selectively targets VEGF receptor 2 tyrosine kinase. Of the 6 patients with CMML in the study, 1 (17%) had stable disease for longer than 6 months. Cytogenetic abnormalities in treated patients were not reported [153]. It is worthwhile to note that aberrant activation of *ROS1*, a tyrosine kinase, was detected in the CD34+ cell compartment for 70% of CMML patients in one recent study [86].

The immunomodulator thalidomide and its derivative lenalidomide have both been used to treat CMML. In one series, thalidomide was studied in MDS patients, and 3 patients with CMML were included. One patient experienced hematologic improvement, with a platelet response [154]. In another study, none of four patients with CMML had a response [155]. A larger study included 13 CMML patients who received thalidomide alone or in combination with arsenic trioxide, topotecan, or ciprofloxacin plus dexamethasone. The overall response rate was approximately 21%; however, individual responses for patients with CMML were not reported [156].

One study combined two investigational therapies for patients with MDS and included 6 patients with CMML. Patients were treated with topotecan at 1.25 mg/m^2 on days 1-5 of a 21-day cycle for three cycles and were then evaluated. If blasts were <5% or had decreased by >50%, the patients were then treated with thalidomide at 100 mg/day (with dose escalation up to 300 mg/day) for up to 1 year. Otherwise, the patients were retreated with topotecan until blast indices had reached the levels required to change the therapy to thalidomide. Of the 6 patients with CMML, 1 (with karyotype 46, XY, del(7)(q11.2)[20]) had a partial response with hematologic improvement in erythroid cells and became transfusion independent. The findings suggested that the combined regimen, which was generally well tolerated, or maintenance therapy with thalidomide once a decrease in blasts is achieved, may be appropriate for selected CMML patients [146].

Two studies that looked at thalidomide in combination with 5-azacytidine or as a part of the TADA regimen (thalidomide, arsenic trioxide, dexamethasone, and ascorbic acid) reported response rates of 50% and 38%, respectively [157, 158]. In the study by Bejanyan et al. the TADA regimen was evaluated also in 15 patients with MDS/MPN-unclassifiable, a large number of difficult-to-classify patients whose clinical characteristics overlap with CMML. In another study, lenalidomide was used to treat CMML-2 in a patient who had a del(5q) cytogenetic abnormality. A single 14-day course of lenalidomide at 25 mg/day, administered in preparation for allogeneic stem cell transplantation, resulted in cytoreduction and blast clearance in the patient [159].

Three studies investigating the histone deacetylase inhibitor valproic acid (VPA) for treatment of MDS and CMML obtained inconclusive results for CMML patients [160-162]. Vorinostat (suberoylanilide hydroxamic acid) is another histone deacetylase inhibitor that was approved by the Food and Drug Administration for cutaneous T-cell lymphoma. It was investigated for treatment of MDS alone, and no CMML patients were included [163].

Notably, the MDS/CMML–derived cell line P39 was inhibited by vorinostat alone (as well as by bortezomib alone) in a preclinical study [164].

As noted, some patients with CMML possess mutations in *JAK2*, suggesting that constitutive activation of the JAK/STAT pathway may be targetable for therapy. The *JAK2* inhibitor ruxolitinib has been tested in a limited number of CMML patients [44]. Additionally, Padron et al. have recently reported a GM-CSF-dependent STAT5 hypersensitivity in up to 90% of CMML patients, with potential therapy targeting GM-CSF and the JAK/STAT pathway [76].

Because CMML cells often carry *RAS* mutations leading to increased RAS protein activity, the RAS-activation pathway has been the target of potential therapeutics [165]. The RAS-activating enzyme farnesyltransferase has been targeted with specific farnesyltransferase inhibitors (FTIs). In the largest multicenter study to date, 35 CMML patients were treated with the FTI lonafarnib at 200-300 mg twice daily. The overall response rate was 29%, with two patients with CMML-2 achieving CR [166]. Another FTI, tipifarnib, has been investigated in phase 1 and 2 trials, as well as in combination with idarubicin and cytarabine for treatment of MDS [167-170]. In a phase 2 study, 17 patients with CMML-1 or CMML-2 received tipifarnib at a dose of 300-600 mg twice daily, and 3 had CR (18%), with a median survival of 14.5 months [170]. Although myelosuppression was the most commonly observed adverse effect with tipifarnib, it is notable that some CMML patients have had rapid onset of leukocytosis with lonafarnib or tipifarnib treatment, which may be akin to leukemia differentiation syndrome [167, 171].

5.5. Conclusions

Although many therapies have been tested against CMML (additional experimental therapies are detailed in Table 3), much work remains to identify optimal treatment for individual patients. In addition, appropriate response criteria have not previously been defined specifically for patients with MDS/MPN, and as criteria are designed, treatments may be better assessed. As the classification of patients with CMML continues to evolve, so will treatment protocols. Stratification based on patient and disease characteristics has become increasingly important to treatment decisions. With the dawn of more sophisticated assays, such as next-generation sequencing, targeted therapy will be directed at patients who would maximally benefit from them. Simultaneously, an increasing understanding of the underlying mechanisms that drive the pathogenesis of this unique disorder will improve the classification, prognostication, and treatment of patients with CMML.

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Table 1

FAB [9, 10] and WHO [3] classifications of CMML.

FAB classification	WHO classification
MDS	MDS/MPD overlap syndrome
PB Monocytes > 1×10^9/L (defining feature)	PB Monocytes > 1×10^9/L
Myeloblasts < 20% in bone marrow	Myeloblasts < 20% in bone marrow
PB blasts < 5%	No Philadelphia chromosome or *BCR-ABL1* fusion gene
Subclassification MD-CMML: WBC ≤ 13×10^9/L MP-CMML: WBC > 13×10^9/L	No rearrangement of *PDGFRA* or *PDGFRB* (excluded especially in cases with eosinophilia) Dysplasia in at least one myeloid lineage. If myelodysplasia is absent or minimal, diagnosis can still be made if the other requirements are present *and* An acquired clonal cytogenetic or molecular genetic abnormality is present *or* The monocytosis has persisted for at least 3 months *and* all other causes of monocytosis have been excluded (e.g. infection, inflammation, malignancy) Subclassification CMML-1: PB blasts < 5%, BM blasts < 10% CMML-2: PB blasts 5-19%, BM blasts 10-19%, or Auer rods present CMML-1 or CMML-2 with eosinophilia: above criteria with PB eosinophils > 1.5×10^9/L

FAB, French-American-British; WHO, World Health Organization, CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; PB, peripheral blood; MD-CMML, myelodysplastic CMML; MP-CMML, myeloproliferative CMML.

Table 2

Prognostic scoring of CMML by CPSS [110] and G-MDAPS [111].

CPSS (0-5 points)			
	Characteristic for score		
Variable	**0**	**1**	**2**
WHO subtype	CMML-1	CMML-2	-
FAB subtype	MD-CMML	MP-CMML	-
CMML-specific cytogenetic risk	Low	Int	High
RBC transfusion dependence	No	Yes	-
Risk groups for overall scores			
Low	0		
Intermediate-1	1		
Intermediate-2	2		
High	3		

G-MDAPS (0-17 points)	
Prognostic factor	**Points**
Performance status ≥ 2	2
Age, yr	
60-64	1
≥ 65	2
Platelets, × 10^9/L	
<30	3
30-49	2
50-199	1
Hemoglobin < 12g/dL	2
Bone marrow blasts, %	
5-10	1
11-29	2
WBC > 20 × 10^9/L	2

G-MDAPS (0-17 points)	
Prognostic factor	**Points**
Karyotype: Chr7 abnormality or ≥ 3 abnormalities	3
Prior transfusion	1

Risk groups for overall scores	
Low	0-4
Intermediate-1	5-6
Intermediate-2	7-8
High	≥9

CMML, chronic myelomonocytic leukemia; CPSS, CMML-specific prognostic scoring system; G-MDAPS, Global MD Anderson Prognostic Scoring system; WHO, World Health Organization; FAB, French-American-British; MD-CMML, myelodysplastic CMML; MP-CMML, myeloproliferative CMML; RBC, red blood cell; WBC, white blood cells; Chr7, chromosome 7.

Table 3

Selected published studies and reports using investigational therapies for CMML.

Reference [#]	Drug class	Specific drug	Other drugs used	Regimen	No. of CMML patients	CMML-1, CMML-2	Age	Cytogenetics/molec info	Nonhematologic toxicities	Response
Beran, 1996 [142]	Topoisomerase I inhibitor	Topotecan	None	2 mg/m^2 cont IV per day × 5 days repeated every 4-8 weeks	25	Not reported	21 patients (84%) ≥ 60 years	Diploid 10 (40%), abnormal 5/7 7 (28%), 11q 2 (8%), other 2 (8%)	Mucositis, GI, neurotoxicity most common	28% CR
Beran, 1998 [143]	Topoisomerase I inhibitor	Topotecan	None	2 mg/m^2 cont IV per day × 5 days repeated every 4-8 weeks	30	Not reported	Including patients with MDS, 83% were > 60 years	Not reported for CMML patients	Mucositis, GI, neurotoxicity most common	27% CR
Beran, 1999 [144]	Topoisomerase I inhibitor	Topotecan	Cytarabine	Topotecan 1.25 mg/m^2 cont IV per day on days 1-5 + cytarabine 1g/m^2 IV over 2 hours on days 1-5	27	Not reported	Median 64 years (range 21-80) for all patients including MDS	Not reported	Mucositis, diarrhea, rash, nausea/vomiting, fever, infection	44% CR
Weihrauch, 2004 [145]	Topoisomerase I inhibitor	Topotecan	Cytarabine	Topotecan 1.25 mg/m^2 cont IV per day on days 1-5 + cytarabine 1g/m^2 IV over 2 hours on days 1-5	1	Not reported	Median 62 years (range 32-75) for all patients including MDS	Not reported	GI, rash, fever, alopecia, pain	Non-CR
Quintas-Cardama, 2006 [172]	Topoisomerase I inhibitor	9-Nitro-camptothecin	None	9-NC 2 mg/m^2 PO daily × 5 d/wk as tolerated	32	26 (81%) CMML-1, 5 (16%) CMML-2	Median 66 years	Diploid, trisomy 8, other reported for responders	GI (reversible)	40% ORR, 16% CR
Ribrag, 2003 [173]	Topoisomerase I inhibitor	CPT-11	None	CPT-11 200 mg/m^2 IV every 2 weeks	5	Not reported	Median 71 years, including patients with MDS (range, 51-77)	Not reported for individual CMML patients	TLS with ARF, invasive fungal infection, GI	1 patient with CMML had disappearance of pleural effusion, splenomegaly and monocytosis but BM blasts > 5%
Kantarjian, 2010 [148]	Deoxycytidine analog	Sapacitabine	None	75 mg PO BID × 7 days every 3-4 weeks	Not reported	Not reported	Median 65 years (range, 35-90), including all patients with CMML, AML, MDS, ALL	Responders: del 13q, diploid, other (noncomplex)	GI, alopecia, fatigue most common	3 patients with h/o CMML responded; CMML→AML: CRp (2.2 mos); MDS-CMML: CR (3.3 mos); MDS-CMML:

Reference [#]	Drug class	Specific drug	Other drugs used	Regimen	No. of CMML patients	CMML-1, CMML-2	Age	Cytogenetics/molec info	Nonhematologic toxicities	Response
										BM CR (2 mos)
Faderl, 2010 [149]	Nucleoside analog	Clofarabine	None	After toxicity evaluations, 20 mg/m^2 PO daily × 5 days, every 4-8 weeks	6	5 (15%) CMML-1, 1 (3%) CMML-2	Median 70 years (range, 53-86), including all patients with MDS, CMML, AML	Not reported	GI, rash, elevated LFTs, fatigue, headache most common	33% CR
Apperley, 2002 [37]	Tyrosine kinase inhibitor	Imatinib	None	400 mg PO daily	3 adults, 1 child	Not reported (PDGFRB subtype)	6, 32, 50, and 68 years	All contained translocations involving Chr 5q33	No significant events reported	100% CR
Magnusson, 2002 [38]	Tyrosine kinase inhibitor	Imatinib	None	400 mg PO daily	1	Not reported (PDGFRB subtype)	29 years	t(5;17)(q33;p13.3)	None	100% CR
Giles, 2003 [153]	Tyrosine kinase inhibitor	Semaxanib	None	145 mg/m^2 IV twice weekly	6	Not reported	Median 66 years (range, 29-85), including all patients with MPD, CMML, CML-BP, AMM	Not reported	Abdominal pain, bone pain, dyspnea, headache, fatigue most common	1 patient (17%) with stable disease >6 months
Strupp, 2002 [154]	Immunomodulator	Thalidomide	None	100-400 mg PO daily	3	Not reported	59, 69, 73 years	Poor, good, and good IPSS risk cytogenetics	Fatigue, obstipation, edema most common	33% hematologic improvement, platelets
Raza, 2001 [155]	Immunomodulator	Thalidomide	None	100-400 mg PO daily	4	Not reported	Median 67 years, including all patients with MDS and CMML	Not reported for individual CMML patients	Fatigue, constipation, dyspnea, edema, dizziness, rash, neuropathy, fever, headache, nausea	0% response
Raza, 2006 [146]	Immunomodulator followed by topoisomerase I inhibitor	Thalidomide	Topotecan	Topotecan 1.25 mg/m^2 on days 1-5 of a 21-day cycle for 3 cycles, and then evaluated. If blasts were less than 5% or had decreased by more than 50%, the patients were then treated with thalidomide 100 mg/day (dose escalated up to 300	6	Not reported	Median 68 years (range, 52-79), including patients with MDS	46, X, Y, del(7) (q11.2) in responding patient	Pain, fatigue, fever, constipation most common	17% (1 patient) PR with hematologic improvement in erythroid cells

Reference [#]	Drug class	Specific drug	Other drugs used	Regimen	No. of CMML patients	CMML-1, CMML-2	Age	Cytogenetics/molec info	Nonhematologic toxicities	Response
				mg/day) for up to 1 year						
Bejanyan, 2011 [158]	Immunomodulator + others	Thalidomide	Arsenic trioxide, dexamethasone, ascorbic acid	TADA regimen: Thalidomide 50 mg/day × 2 weeks, then 100 mg/day × 6 months; ATO 0.25 mg/kg × 5 days, then 0.25 mg/kg twice per week × 11 weeks; Dex 4 mg/day × 5 days every 4 weeks; AA 1000 mg PO 2-3 hours prior to each ATO dose	8	All 8 had CMML-1	Median 66 years, including patients with MDS/MPN-u, PMF, and splenomegaly	Not reported for individual CMML patients	Fatigue, edema, cough, dyspnea, GI, neuropathy, infection, rash	38% overall response (1 PR and 2 stable disease)
Raza, 2008 [157]	Immunomodulator + hypomethylator	Thalidomide	5-Azacytadine	5-Azacytadine 75 mg/m^2 SC daily × 5 days every 28 days + thalidomide 50-100 mg PO daily	4	Not reported	Median 72 years (range, 49-84), including patients with MDS, AML	Diploid: 2 patients; 46,xy,r(18)(p11.3q23)[10]/46,xy[10] and 47,xx,18[13]/46,xx[7] in the other 2	Fever, DVT, GI, infection	50% with major hematologic improvement (both in patients with diploid CGs)
Platzbecker, 2007 [159]	Immunomodulator	Lenalidomide	None	25 mg/day × 14 days	1	CMML-2	66 years	Single del(5q)(q31); FISH revealed loss of *CSF1R* gene at 5q33, and not *EGR1*	None reported	Hematologic improvement
Buckstein, 2014 [174]	Immunomodulator	Lenalidomide	Melphalan	Lenalidomide 10 mg PO daily; Melphalan 2 mg PO daily for 21 days of a 28-day cycle	12	10 (83%) CMML-1; 2 (17%) CMML-2	Median 73 (range, 52-87), including patients with MDS	Not reported for individual CMML patients	Infection, neurological	25% overall response (1 CR, 1 HI-platelets, 1 HI-erythroid); all 3 responders had proliferative CMML-1
Cambier, 1996 [175]	Retinoid	All-trans retinoic acid	+/− Hydroxyurea (for differentiation syndrome in 6 patients)	45 mg/m^2 daily	10	Not reported	Median 66 years (range 57-74)	Not reported	Differentiation syndrome	40% had reduction in transfusion requirement or increases in platelet count
Kuendgen, 2004 [160]	Histone deacetylase inhibitor +/− retinoid	Valproic acid	+/− ATRA	VPA administered PO with dose escalation to reach	1	Not reported	68 years	Normal	Vertigo, tremor	Progressive disease after 4 months

Reference [#]	Drug class	Specific drug	Other drugs used	Regimen	No. of CMML patients	CMML-1, CMML-2	Age	Cytogenetics/molec info	Nonhematologic toxicities	Response
				serum concentrations of 346-693 μM during months 1-4; ATRA 80 mg/m^2 PO daily in 2 divided doses on days 1-7 every other week during months 3-4						
Siitonen, 2007 [161]	Histone deacetylase inhibitor + retinoid	Valproic acid	13-cis retinoic acid + 1,25-dihydroxyvitamin D3	VPA administered PO with dose escalation to reach serum concentrations of 500-700 μmol/L; 13-cis retinoic acid 10 mg PO BID; VD3 1 μg PO daily	4	3 (75%) CMML-1, 1 (25%) CMML-2	73, 74, 76 years (CMML-1); 79 years (CMML-2)	CMML-1 patients: normal; CMML-2 patient: t(1;3), +8	Cheilitis, dry skin, fatigue, elevated LFTs, pneumonitis	CMML-2 patient had stable disease; CMML-1 patients: 2 with stable disease and 1 with hematologic improvement
Voso, 2009 [162]	Histone deacetylase inhibitor + hypomethylator	Valproic acid	5-Azacytadine +/− ATRA	VPA 600 to 1,500 mg PO on day 0 to reach a final plasma concentration of >50 μg/mL; then 5-AZA was added at a standard dose of 75 mg/m^2 SC daily × 7 days every 4 weeks × 8 cycles. In cases of minor response, stable disease, or failure after four cycles, ATRA was added at 30 mg/m^2 PO daily on days 8 to 27 × 4 cycles	4	Not reported	Median 70 years (range, 53-83) including patients with MDS	Not reported for individual CMML patients	Allergy, cardiovascular, GI, dyspnea, elevated LFTs	Not reported for individual CMML patients. CR/PR rate for patients who completed 8 cycles (n=26) was 31%.

Reference [#]	Drug class	Specific drug	Other drugs used	Regimen	No. of CMML patients	CMML-1, CMML-2	Age	Cytogenetics/molec info	Nonhematologic toxicities	Response
Ravoet, 2008 [176]	Farnesyltransferase inhibitor	Lonafarnib	None	200 mg PO BID	2	Not reported	63 and 77 years	Both normal	GI, fever, elevated LFTs	Both with stable disease
Feldman, 2008 [166]	Farnesyltransferase inhibitor	Lonafarnib	None	200-300 mg PO BID	35	11 were reported as MDS-CMML and 24 as MPD-CMML	Median 70 years (range, 44-86) including patients with MDS	Not reported for individual CMML patients	GI, dyspnea, weakness, dehydration, fever, hypokalemia	29% overall response (4 HI in MDS-CMML; 3 HI, 1 PR, 2 CR in MPD-CMML)
Kurzrock, 2003 [167]	Farnesyltransferase inhibitor	Tipifarnib	None	Increased from 300 mg PO BID on days 1-21 of a 28-day cycle	10	Not reported	Median 66 years (range 50-83), including patients with MDS	Not reported for individual CMML patients	Fatigue, rash, GI, elevated LFTs, bone pain	30% in CMML patients (1 HI and 2 PR)
Fenaux, 2007 [170]	Farnesyltransferase inhibitor	Tipifarnib	None	Increased from 300 mg PO BID on days 1-21 of a 28 day cycle	17	8 (47%) CMML-1, 9 (53%) CMML-2	Median 67 years (range 39-86), including patients with MDS	Not reported for individual CMML patients	Fever, infection, rash, fatigue	18% CR (1 CMML-1 and 2 CMML-2 patients); individual HI, PR for CMML patients not reported, but median survival for all CMML patients was 14.5 months
Borthakur, 2007 [177]	Farnesyltransferase inhibitor	FTS (s-trans, transfarnesylthiosalicylic acid)	None	200-600 mg PO BID on days 1-21 of a 28-day cycle	1	Not reported	Median 74 years (range 57-85), including patients with AML, MDS, and CML	Not reported	Diarrhea	HI in CMML patient
Eghtedar, 2010 [178]	JAK2 inhibitor	Ruxolitinib	None	25 mg PO BID	4	Not reported	Median 69 years (range, 45–88), including patients with sAML, AML, ALL, MDS, and CML	Not reported	Elevated LFTs	75% (3 CMML patients) had clinical benefit; 1 of these (with JAK2 mutation) had reduction of BM blasts <5%

molec, molecular; cont, continuous; IV, intravenously; 5/7, chromosome 5 or 7; GI, gastrointestinal; 9-NC, 9-Nitro-camptothecin; PO, orally; ORR, overall response rate; TLS, tumor lysis syndrome; ARF, acute renal failure; BID, twice daily; ALL, acute lymphocytic leukemia; del, deletion; h/o, history of; CRp, complete remission without recovery of platelets; LFTs, liver function tests; Chr, chromosome; AMM, agnogenic myeloid metaplaisia; IPSS, international prognostic scoring system for MDS risk; PR, partial remission; ATO, arsenic trioxide; Dex, dexamethasone; AA, ascorbic acid; MDS/MPN-u, MDS/MPN unclassifiable; PMF, primary myelofibrosis; SC, subcutaneously; DVT, deep venous thrombosis; CGs, cytogenetics; FISH, fluorescent in situ hybridization; ATRA, all-trans retinoic acid; VPA, valproic acid; VD3, 1,25-dihydroxyvitamin D3; 5-AZA, 5-azacytidine; HI, hematologic improvement; sAML, post-myeloproliferative disorder acute myeloid leukemia; CML, chronic myeloid leukemia.