Curr Hematol Malig Rep (2015) 10:292–302
DOI 10.1007/s11899-015-0271-4

MYELODYSPLASTIC SYNDROMES (D STEENSMA, SECTION EDITOR)

Chronic Myelomonocytic Leukemia: a Genetic and Clinical Update

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Published online: 28 June 2015

Abstract Chronic myelomonocytic leukemia (CMML) is a clonal stem cell disorder, characterized by peripheral blood monocytosis and overlapping features between myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs). Clonal cytogenetic changes are seen in up to 30 % patients, while approximately 90 % have detectable molecular abnormalities. Most patients are diagnosed in the seventh decade of life. Gene mutations in ten-eleven translocation (TET) oncogene family member 2 (*TET2*) (60 %), *SRSF2* (50 %), *ASXL1* (40 %), and *RAS* (20-30 %) are frequent, with only frame shift and nonsense *ASXL1* mutations negatively impacting overall survival. With the lack of formal guidelines, management and response criteria are often extrapolated from MDS and MPN. Contemporary molecularly integrated CMML-specific prognostic models include the Groupe Francais des Myelodysplasies (GFM) model and the Molecular Mayo Model, both incorporating *ASXL1* mutational status. Hypomethylating agents and allogeneic stem cell transplant remain the two most commonly used treatment strategies, with suboptimal results. Clinical trials exploiting epigenetic and signal pathway abnormalities, frequent in CMML, offer hope and promise.

This article is part of the Topical Collection on *Myelodysplastic Syndromes*

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Keywords CMML · Prognosis · *ASXL1* · Hypomethylating agents

Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disorder characterized by overlapping features of both myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs) [1]. In the 2008 World Health Organization (WHO) classification of hematological malignancies, CMML is categorized as an MDS/MPN overlap syndrome, with other disorders in this group being the following: juvenile myelomonocytic leukemia (JMML), atypical chronic myeloid leukemia (CML), MDS/MPN-unclassifiable, and refractory anemia with ring sideroblasts and thrombocytosis (RARS-T; currently a provisional entity).

The 2008 WHO criteria define CMML as a disorder characterized by the following: (a) persistent peripheral blood (PB) monocytosis $>1\times10^9$/l, (b) absence of the Philadelphia chromosome and the *BCR-ABL1* fusion oncogene, (c) absence of the *PDGFRA* or *PDGFRB* gene rearrangements, (d) less than 20 % blasts and promonocytes in the PB and bone marrow (BM), and (e) dysplasia involving one or more myeloid lineages [1]. If myelodysplasia is absent or minimal, the diagnosis of CMML can still be made if the other requirements are met and: an acquired, clonal, or molecular genetic abnormality is present in the hematopoietic cells or if the monocytosis has persisted for at least 3 months and other causes of monocytosis have been excluded [1, 2••]. Additionally, CMML is further subclassified into CMML-1 (<5 % circulating blasts and <10 % BM blasts) and CMML-2 (5–19 % circulating blasts, 10–19 % BM blasts, or when Auer rods are present irrespective of the blast count), with the median overall survival (OS) being approximately 20 and 15 months,

respectively [3, 4••, 5]. The median age at diagnosis is approximately 71–74 years, with a male preponderance [6–8]. Therapy-related CMML cases have been described and, like their MDS counterparts, are associated with poor outcomes [9].

The platelet-derived growth factor receptors alpha and beta (*PDGFRA*-chromosome *4q12* and PDGFR*B*- chromosome *5q31-q32*) are type III receptor tyrosine kinases. Abnormal chromosomal translocations involving these growth factor receptors have been associated with myeloid neoplasms characterized by prominent blood eosinophilia and marked responsiveness to imatinib mesylate [10, 11]. At times, *PDGFR*-rearranged myeloid neoplasms can be associated with monocytosis and BM dysplasia, but given their unique responsiveness to imatinib, these are no longer classified as CMML. Patients presenting with a clinical phenotype of CMML with eosinophilia should be assessed for the t(5;12)(q31-q32;p13), giving rise to the *ETV6*(*TEL*)-*PDGFRB* fusion oncogene [12]. The association between monocytosis and *PDGFRA* rearrangements is an uncommon occurrence [13].

CMML Biology

Cytogenetic Abnormalities in CMML

Clonal cytogenetic abnormalities are seen in 20–30 % of patients with CMML [3, 7, 14•, 15]. Common alterations include the following: trisomy 8, -Y, abnormalities of chromosome 7, trisomy 21, and complex karyotypes [14•]. Based on these findings, the Spanish cytogenetic risk stratification system was developed, categorizing patients into three groups: high risk (trisomy 8, chromosome 7 abnormalities, or complex karyotype), intermediate risk (all chromosomal abnormalities, except for those in the high- and low-risk categories), and low risk (normal karyotype or -Y), with 5-year OS of 4, 26, and 35 %, respectively [14•]. Similar to MDS, the adverse prognostic impact of monosomal karyotype (MK) in CMML was described, predicting an inferior OS in comparison to complex karyotypes without monosomies [16, 17]. Unlike MDS, sole del(5q) is very infrequent in CMML [18].

Recently, a single institutional CMML database, with 417 patients, was analyzed for cytogenetic abnormalities [15]. While the Spanish cytogenetic risk stratification system was found to be effective, patients with +8 were found to have a median OS of 22 months, similar to the intermediate-risk group, but significantly better than the high-risk group (14 months). By moving +8 to the intermediate-risk group, they demonstrated a more effective cytogenetic risk stratification system, predicting for both, OS and leukemia-free survival (LFS) [15]. Additionally, in a large international collaborative study, 409 patients with CMML were analyzed for cytogenetic and molecular abnormalities [268 (66 %) and 141 (34 %) from the Mayo Clinic and French Consortium, respectively] [18]. Thirty percent displayed an abnormal karyotype; common abnormalities being +8 (23 %), -Y (20 %), -7/7q- (14 %), 20q- (8 %), +21 (8 %), and der(3q) (8 %) [18]. A stepwise survival analysis resulted in three distinct cytogenetic risk categories: high (complex and MKs), intermediate (all abnormalities not in the high- or low-risk groups), and low (normal, sole -Y and sole der (3q)) with median OS of 3 (hazard ratio (HR) 8.1, 95 % confidence interval (CI) 4.6–14.2), 21 (HR 1.7, 95 % CI 1.2–2.3), and 41 months, respectively [18].

Molecular Abnormalities in CMML

The advent of next-generation sequencing technology has identified molecular abnormalities in approximately 90 % of patients with CMML [19, 20••]. These abnormalities can be classified into the following categories:

1. Mutations involving epigenetic regulator genes: ten-eleven translocation (TET) oncogene family member 2 (*TET2*) (~60 %), *DNMT3A*, *IDH1*, and *IDH2*
2. Mutations involving chromatin regulation: *ASXL1* (~40 %) and enhancer of zeste homolog 2 (*EZH2*)
3. Mutations involving the splicing machinery: *SF3B1*, *SRSF2* (~50 %), *SF3A1 U2AF1*, *ZRSR2*, *PRPF30B*, *SF1*
4. Mutations involving DNA damage response genes: *Tp53* (<1 %), *PFH6*
5. Mutations in signal transduction and cellular/receptor tyrosine kinase pathways: *JAK2*, *KRAS*, *NRAS*, *CBL*, *FLT3*, *RUNX1*

TET2 Mutations

TET2 is a tumor suppressor gene on chromosome 4q24 [21]. The incidence of *TET2* mutations in CMML is ~60 % [22]. As reported for *TET1*, *TET2* converts 5-methyl-cytosine to 5-hydroxymethyl-cytosine in embryonic stem cells, and thus, mutations of *TET2* are proposed to contribute to leukemogenesis by altering epigenetic regulation of transcription through DNA methylation [21]. The exact mechanism and the extent to which *TET2* mutations affect DNA methylation remain in question. Ko et al. reported that loss of 5-methyl-cytosine (hypomethylation) was a remarkable characteristic in CMML patients with *TET2* mutations and found 2510 differentially hypomethylated regions and only two hypermethylated regions [23]. In contrast, Figueroa et al. studied *TET2* mutant leukemic cells and identified a hypermethylation phenotype, including 129 differentially methylated regions [24]. Yamazaki et al., using bisulfite pyrosequencing, confirmed that *TET2* mutations affect global methylation in

CMML but hypothesized that most of the changes were likely to be outside gene promoter regions [21]. Although *TET2* mutations are widely prevalent in CMML, they have not been shown to independently impact either OS or LFS [22]. Similar to MDS, where clonal *TET2* mutations in the absence of clonal *ASXL1* mutations predict for response to hypomethylating agents (HMA) [25], at least in young CMML patients (age <65 years), there seems to be a similar relationship [26].

ASXL1 and EZH2 Mutations

The *ASXL1* (additional sex comb-like 1) gene maps to chromosome 20q11 and regulates chromatin by interacting with the polycomb group repressive complex proteins (PRC1 and PRC2) [27]. *ASXL1* mutations are seen in ~40 % of patients with CMML [22, 5]. In a seminal paper, Abdel-Wahab et al. demonstrated that *ASXL1* mutations resulted in loss of PRC2-mediated histone H3 lysine 27 (H3K27) trimethylation [28]. Through integration of microarray data with genome-wide histone modification ChIP-Seq (chromatin immunoprecipitation) data, they identified targets of *ASXL1* repression including the posterior *HOXA* cluster that is known to contribute to myeloid transformation. In addition, they showed that *ASXL1* associates with PRC2 and that loss of *ASXL1* in vivo collaborates with *NRAS*G12D to promote myeloid leukemogenesis [28]. The *EZH2* gene, located on chromosome 7q35–q36, encodes for the PRC2 protein, a highly conserved enzyme which serves as a histone H3K27 methyltransferase. *EZH2* mutations are infrequent (~5 %) in CMML [22]. Thus far, both of these mutations have been associated with an independent prognostic impact, in some, but not all studies [29, 22, 5]. The specific prognostic role of *ASXL1* mutations in CMML will be further discussed.

Spliceosome Component Mutations

Spliceosome component mutations (*SRSF2*, *SF3B1*, and *U2AF1*) affect pre-messenger RNA (mRNA) splicing and result in diverse clinicopathological effects. They are involved in the 3′ splice site recognition of pre-mRNA, including abnormal/alternative splicing. The U2 auxiliary factor that consists of the U2AF65-U2AF1 heterodimer, establishes physical interaction with SF1 and a serine/arginine-rich protein such as SRSF1 or SRSF2, resulting in recognition of the 3′ splice site and its nearby polypyrimidine tract [30]. This leads to the subsequent recruitment of U2 snRNP, containing SF3A1 and SF3B1 to establish the splicing A complex [30]. *SRSF2* mutations are very common (~50 %) in CMML and are associated with increased age, less-pronounced anemia, and a diploid karyotype [7]. Thus far, in CMML, *SRSF2* mutations have not demonstrated an independent prognostic impact for either OS or LFS [31, 7, 22]. *SF3B1* mutations have a high prevalence (~80 %) in patients with MDS and ring sideroblasts (RS) [32] and can also be seen in patients with CMML and RS (<10 %) [7]. However, these mutations do not influence either the OS or LFS [33, 34]. Similarly, *U2AF1* mutations are seen in ~10 % of patients with CMML and have thus far lacked an independent prognostic effect [30].

Signal Pathway Mutations

Signal pathway mutations are common in CMML: *JAK2*V617F (~10–15 %), *RAS* (*KRAS* and *NRAS* ~20–30 %), *RUNX1* (~15 %), and *CBL* (~10–20 %) [35, 22]. *RAS* mutations are often associated with a MPN-like phenotype with monocytosis [36]. Although univariate analysis studies with *RAS* mutations have demonstrated inferior outcomes in CMML, these findings have not been substantiated in multivariable models [3, 22]. The *CBL* gene codes for an E3 ubiquitin ligase involved in degradation of activated receptor tyrosine kinases. RING finger domain (RFD) mutations of *CBL* are frequently associated with UPD11q (uniparental disomy) and have been reported in 10–20 % of patients with CMML [22, 35]. *RUNX1* is essential for normal hematopoiesis, and mutations can be seen in 10–15 % of patients with CMML [22, 35]. Although these mutations do not impact OS, there is a trend toward a higher risk of AML progression [37]. Recently, in vivo studies have demonstrated granulocyte monocyte-colony-stimulating factor (GM-CSF)-dependent pSTAT5 sensitivity in CMML [38].

SETBP1 Mutations

SETBP1, located on chromosome 18q21.1, encodes the SET-binding protein 1, a binding partner for the multifunction SET protein. This protein is involved in apoptosis, transcription, and nucleosome assembly [39]. The proposed functional outcome of this interaction is based on in vitro studies that demonstrate a protection of SET protein from protease cleavage that results in inhibition of protein phosphatase 2A activity, leading to higher rates of cell proliferation. In CMML, *SETBP1* mutations have a frequency of 5–10 %, with some [40, 39], but not all studies demonstrating prognostic relevance [4••].

CMML Prognostic Scoring Systems

Numerous prognostic models have attempted to risk stratify patients with CMML. In this regard, the value of Bournemouth, Lille, and the International Prognostic Scoring Systems (IPSS) is limited, as they were designed primarily for patients with MDS, excluding CMML patients with a proliferative phenotype [41, 11, 42]. The MD Anderson Prognostic Scoring System (MDAPS) is CMML-specific and identified a hemoglobin level <12 g/dl, presence of

circulating immature myeloid cells (IMC), absolute lymphocyte count (ALC) >2.5×10^9/l, and ≥10 % BM blasts as independent predictors for inferior survival [3]. This model identified four subgroups of patients with median survivals of 24, 15, 8, and 5 months, respectively [3]. The MDAPS was subsequently applied to 212 CMML patients in the Dusseldorf registry; in a univariate analysis, circulating IMC had no prognostic impact, while on multivariable analysis, elevated LDH, BM blast count >10 %, male gender, hemoglobin <12 g/dl, and ALC >2.5×10^9/l were independently prognostic [43].

In 2008, the Global MDAPS was developed for patients with de novo MDS, secondary MDS, and CMML (n=1915) [44]. On a multivariable analysis, independent prognostic factors included the following: older age, poor performance status, thrombocytopenia, anemia, increased BM blasts, leukocytosis (>20×10^9/l), chromosome 7 or complex cytogenetic abnormalities, and a prior history of red blood cell transfusions [44]. This model identified four prognostic groups with median survivals of 54 (low), 25 (intermediate-1), 14 (intermediate-2), and 6 months (high), respectively [44]. The CMML-specific prognostic scoring system (CPSS) was developed in a large cohort of CMML patients (n=558) and identified the following four variables as being prognostic for both OS and LFS: French-American-British (FAB) and WHO CMML subtypes, red blood cell transfusion dependency, and the Spanish cytogenetic risk stratification system [14•, 8]. One point was accorded for each variable, with the exception of high-risk cytogenetics which earned two points, and four risk categories were determined: low (0 points), intermediate-1 (1), intermediate-2 (2–3), and high risk (4–5). Median OS was 72, 31, 13, and 5 months for each of the categories, respectively [8].

The discovery of molecular aberrations in CMML has resulted in the development of models inclusive of these abnormalities. A Mayo Clinic study (n=226) analyzed several parameters, including *ASXL1* mutations, and on multivariable analysis, risk factors for survival included hemoglobin <10 g/dl, platelet count <100×10^9/l, absolute monocyte count (AMC) >10×10^9/l, and circulating IMC [5]. *ASXL1* mutations did not impact either the OS or the LFS. The study resulted in the development of the Mayo prognostic model, with three risk categories, low (0 risk factor), intermediate (1 risk factor), and high (≥2 risk factors), with median survivals of 32, 18.5, and 10 months, respectively [5]. The Groupe Francais des Myelodysplasies (GFM), however, demonstrated an adverse prognostic effect for *ASXL1* mutations in 312 patients with CMML; additional risk factors on multivariable analysis included age >65 years, white blood count (WBC) >15×10^9/l, platelet count <100×10^9/l, and hemoglobin level <10 g/dl in females and <11 g/dl in males [22]. The GFM prognostic model assigns three adverse points for WBC >15×10^9/l and two adverse points for each one of the remaining risk factors, resulting in a three-tiered risk stratification: low (0–4 points), intermediate (5–7), and high (8–12), with respective median survivals of 56, 27.4, and 9.2 months [22]. It should be noted that all nucleotide variations (missense, nonsense, and frame shift) were regarded as *ASXL1* mutations in the Mayo study [5], whereas only nonsense and frame shift *ASXL1* mutations were considered in the French study [22]. To further clarify the prognostic relevance of *ASXL1* mutations, an international collaborative cohort of 466 patients was analyzed [18]. In univariate analysis, survival was adversely affected by *ASXL1* (nonsense and frame shift) but not *SETBP1* mutations. In multivariable analysis, *ASXL1* mutations, AMC >10×10^9/l, hemoglobin <10 g/dl, platelets <100×10^9/l, and circulating IMC were independently predictive of shortened survival. A regression coefficient-based prognostic model based on these five risk factors delineated high (≥3 risk factors; HR 6.2, 95 % CI 3.7–10.4) intermediate-2-risk (two risk factors; HR 3.4, 95 % CI 2.0–5.6), intermediate-1-risk (one risk factor; HR 1.9, 95 % CI 1.1–3.3), and low-risk (no risk factors) categories with median survivals of 16, 31, 59, and 97 months, respectively. This model is referred to as the Molecular Mayo Model.

Management of CMML

Given the inherent similarities with MDS and MPN, management and response evaluation for patients with CMML is often extrapolated from these diseases. The management of cytopenias is similar to lower-risk MDS patients and includes the use of erythropoiesis-stimulating agents (ESA) and transfusion-based supportive care [45•, 46].

Management of Cytopenias

Commercially available ESA include recombinant human erythropoietin (rh-EPO) and darbepoetin. Response rates in lower-risk MDS/CMML patients range from 30 to 60 %, with the median duration of response being ~24 months [47–49]. Parameters predictive of ESA response include the following: low transfusion burden (<2 units a month), use of a fixed-dose versus weight-based EPO regimen, shorter time from diagnosis to starting treatment, and a lower baseline serum EPO level (<500 IU/ml) [47, 48]. Most responses to ESA occur within 8 weeks of treatment. These agents have to be used with caution in CMML patients with a proliferative phenotype, given the inherent risk for spontaneous splenic rupture.

Two first in-class agents targeting late stages of erythropoiesis are currently in development for MDS and CMML. Sotatercept (ACE-011), a recombinant fusion protein containing the extracellular domain of the human activin receptor IIA, binds a variety of TGF-B superfamily ligands [50]. A phase II, dose finding study demonstrated an erythroid response in 40 % of lower-risk transfusion-dependent MDS patients

resistant to ESA [51]. Notably, 19 of 44 patients with high transfusion burden responded with a greater than 4 units/8 week RBC transfusion burden reduction. No data has been presented on the CMML subset of this study as of yet. ACE-536 is another recombinant fusion protein containing the extracellular domain of the human activin receptor IIB. A phase II study assessing low- versus high-transfusion-burden MDS patients (<4 transfusion in the preceding 8 weeks versus ≥4) demonstrated that six of seven patients achieved RBC transfusion independence for more than 8 weeks in the low-transfusion-burden group. In the high-transfusion-burden group, 6 of 19 patients had a greater than 50 % reduction in transfusion requirements [52]. These are exciting prospects for transfusion-dependent CMML patients.

Eltrombopag, a small molecule agonist of c-mpl (megakaryocyte receptor), has been investigated in lower-risk MDS, and preliminary results of two phase II placebo-controlled trials have demonstrated a durable platelet response of 24 and 29 % with no evidence of increasing blast percentage [53, 54]. Success in the setting of autoimmune dysfunction and thrombocytopenia has resulted in off-label use of this agent for patients with CMML [55]. The current status and preliminary response data for investigative agents in CMML has been outlined in Table 1.

Management of Proliferative Disease

Hydroxyurea is the mainstay for management of proliferative CMML. In a prospective randomized study, Wattel et al. compared hydroxyurea to oral etoposide in 105 patients [56]. After a median follow-up of 11 months, 60 % of patients in the hydroxyurea arm responded compared to 36 % in the etoposide arm. Median OS was statistically superior in the hydroxyurea arm (20 months versus 9 months). Several other trials evaluated agents such as low-dose cytarabine with or without the use of *all-trans* retinoic acid [57–59], topotecan [60, 61], 9-nitro-campothecin (a novel topoisomerase inhibitor) [62], valproic acid (histone deacetylase inhibitor) [63], and lonafarnib (farnesyltransferase inhibitor) [64] in the treatment of CMML. Collectively, response rates in these trials were disappointing and treatment was associated with significant toxicities.

Epigenetic Modifying Agents

Hypomethylating agents (HMA) such as 5-azacytidine (AZA) and decitabine (DAC) have been approved for the management of higher-risk MDS patients. Several phase II studies have now been completed using HMA in CMML [6, 34, 65–71]. A complete list of the studies is shown in Table 2. The overall response rates range from 25 to 70 %, and median OS ranges from 12 to 37 months. Unfortunately, the retrospective nature of the vast majority of the studies along with the lack of a comparator arm makes it difficult to draw cross-study conclusions.

Histone deacetylase inhibitors (HDACi) assist in the remodeling of chromatin and play a key role in epigenetic regulation of gene expression [2••]. This has prompted combination therapy with HMA and immunomodulatory agents due to postulated synergistic effects [72]. A randomized phase II intergroup study (S1117) evaluated AZA + lenalidomide, AZA + vorinostat (HDACi), versus AZA monotherapy in MDS and CMML [73]. The median follow-up was 9 months, and no statistically significant difference was seen in response rates across all three arms. Other HDACi currently undergoing clinical trial evaluation include mocetinostat and pracinostat. An additional strategy has been the reformulation of HMA. High levels of cytidine deaminases in the liver and gastrointestinal tract result in rapid elimination of HMA when administered orally. A second-generation HMA, SGI-110, is a reformulation of DAC coupled with deoxyguanosine giving it a significantly prolonged half-life by protection from deamination [74]. A phase II study in treatment-naive and pre-treated patients (20 % CMML) resulted in a complete remission (CR and marrow CR) rate of ~20 % [75]. Red cell transfusion independence of at least 8 weeks was achieved in 32 % of both treatment groups. Alternative mechanisms of cytidine deaminase inhibition are also being investigated with oral DAC and E7727, a novel oral cytidine deaminase inhibitor (NCT02103478-www.clinicaltrials.gov).

Hematopoietic Stem Cell Transplantation

Allogeneic stem cell transplantation (HSCT) remains the only curative option for patients with CMML. This modality is, however, fraught with complications including acute and chronic graft versus host disease (GVHD), nonrelapse mortality, and post-transplant disease relapse. There, unfortunately, exists no prospective data analyzing the risks and befits for HSCT in CMML. The numbers of CMML patients in retrospective series have ranged from 8 to 283, with the median ages ranging from 50 to 56 years. The response rates in these studies have ranged from 17 to 50 % and treatment-related mortality from 12 to 52 % [76–83]. The 10-year OS of 85 patients who underwent HSCT at Fred Hutchinson Cancer Center was 40 %. A multivariable model identified increasing age, higher SCT comorbidity index, and poor-risk cytogenetics to be associated with increased mortality and reduced relapse-free survival (RFS) [76]. The European Group for Blood and Marrow Transplantation (EBMT) reported an OS of 42 % for 283 patients with CMML that underwent HSCT. None of the baseline factors including the conditioning regimen, age, disease status at transplant, cytogenetics, donor-recipient gender match, HLA type of donor, stem cell source, T cell depletion, or the development of GVHD affected the RFS or OS [82]. A recent application of the CPSS in the

Table 1 Investigational agents in chronic myelomonocytic leukemia

Reference	*N* (population)	Median age (years, range)	Phase of study	Treatment regimen	Response rates	Toxicity
Komrokji et al. [51]	54 (MDS)	71 (56–86)	II	Sotatercept (ACE-011) 0.1–1 mg/kg SQ once every 3 weeks.	HI-E, 40 % RBC-TI at 8 weeks: LTB, 67 %; HTB, 11 %	Fatigue (11 %), headache (9.3 %), anorexia (7.4 %), nausea (7.4 %)
Pltazbecker et al. [52]	26 (MDS)	71 (27–88)	II	Luspatercept (ACE-536) 0.125–1.75 mg/kg SQ once every 3 weeks.	RBC-TI at 8 weeks: LTB, 86 %; HTB, 26 %	Diarrhea, bone pain, fatigue, muscle spasms, myalgia, nasopharyngitis
Platzbecker et al. [85]	98 (AML, MDS)	NR	I/II	Eltrombopag 50 mg daily with potential increase up to 300 mg daily. Most received the maximum dose.	Platelet-TI (8 weeks), 38 %	Sepsis, pyrexia, febrile neutropenia, pneumonia
Navada et al. [86]	18 (CMML=1)	70.5 years	I/II	Rigosertib dose escalating, days 1–21 (MTD 560/280 mg) + AZA 75 mg/m^2 days 8–14; cycle=28 days	One patient RBC-TI and five patients with decreased RBC and platelet transfusion needs	Constipation, diarrhea, nausea, fatigue, hypotension, pneumonia
Sekeres et al. [73]	276 (MDS, CMML=50)	70 (28–93)	II	AZA 75 mg/m^2 days 1–7 or AZA + LEN 10 mg/day days 1–21 or AZA + VOR 300 mg BID days 3–9; cycle=28 days	ORR (CMML pts): AZA, 33 % AZA + LEN, 53 % (p=0.15) AZA + VOR, 12 % (p=0.41)	AZA/AZA + LEN/AZA + VOR; febrile neutropenia, 10:13:13 %; infection, 2:3:3 %; GI disorders, 4:11:23 %
Garcia-Manero et al. [87]	14 (AML)	77 (69–84)	II	AZA 75 mg/m^2 days 1–7 or days 1–5, 8, 9 SQ or IV + Pracinostat 60 mg PO thrice weekly for 3 weeks; cycle=28 days	CR + CRi + MLFS, 57 %	Neutropenic fever, thrombocytopenia, nausea, fatigue, anemia
Garcia-Manero et al. [75]	102 (MDS, CMML=22)	Low dose=71.7; high dose=72.5	II	SGI-110 60 or 90 mg/m^2 SQ days 1–5; cycle=28 days	CR+ mCR (60 mg/m^2), 19 % CR + mCR (90 mg/m^2), 22 %	Thrombocytopenia, pneumonia (both slightly higher in the 90 mg/m^2 arm but not statistically different).
Stein et al. [88]	48 (advanced hematologic malignancies)	NR	I	PO, dose escalating: AG-221 30 mg BID through 150 mg BID and 200 mg once daily	ORR, 56 %	NR
Pollyea et al. [89]	14 (advanced hematologic malignancies)	73	I	PO, dose escalating: AG-120 100 mg BID, 300–800 mg once daily	ORR, 50 %; CR, 29 %	QTc prolongation

MDS myelodysplastic syndrome, *AML* acute myeloid leukemia, *NR* not reported, *SQ* subcutaneously, *MTD* maximum tolerated dose, *AZA* azacitidine, *RBC-TI* red blood cell transfusion independent, *LEN* lenalidomide, *VOR* vorinostat, *IV* intravenous, *PO* orally, *BID* twice daily, *HI-E* hematologic improvement—erythroid, *LTB/HTB* low/high transfusion burden, *ORR* overall response rate, *CR* complete remission, *CRi* complete remission with incomplete blood count recovery, *MLFS* morphologic leukemia-free state, *mCR* marrow complete remission

Table 2 Use of hypomethylating agents in chronic myelomonocytic leukemia

Reference	*N*	Median age (years, range)	Phase of study	Treatment regimen	Response rates	Toxicity	Median survival (months)	Progression to acute myeloid leukemia
Aribi [34]	19	66 (44–82)	II	DEC 100 mg/m^2 per course in three different schedules; cycle=28 days	CR, 58 % HI, 11 %	Myelosuppression-related complications, 8 %	19	NR
Wijermans [70]	31	71 (53–81)	II	DEC 15 mg/m^2 over 4 h IV TID on three consecutive days (total= 135 mg/m^2 per course); cycle=42 days	CR, 10 % PR, 16 % HI, 19 %	Nausea, vomiting, pneumonia, mortality due to sepsis, 3 %	15	NR
Costa [66]	38	70 (36–83)	II	AZA 75 mg/m^2 days 1–7 or 100 mg/m^2/day days 1–5; cycle=28 days	CR, 11 % PR, 3 % HI, 25 %	Pneumonia, mortality due to sepsis, 3 %	12	NR
Garcia-Manero [68]	41 (CMML=4)	70 (31–91)	I	AZA 75 mg/m^2 SQ days 1–7 for 1 cycle, followed by oral AZA daily, 120 to 600 mg, on the first 7 days of each cycle; cycle=28 days	Pre-treated ORR, 35 % Treatment-naive ORR, 73 %	Diarrhea, nausea, vomiting, febrile neutropenia, fatigue	NR	NR
Braun [65]	39	71 (54–88)	II	DEC 20 mg/m^2 IV days 1–5; cycle=28 days	CR, 10 % PR, 20 % HI, 8 % ORR, 38 %	Neutropenia and thrombocytopenia (36 %), severe infection (20 %)	18	NR
Thorpe [69]	10	66 (41–76)	II	AZA 75 mg/m^2 days 1–7 or AZA 100 mg/m^2 days 1–5; cycle=28 days	CR, 20 % HI, 40 % ORR, 60 %	Thrombocytopenia, pneumonia (20 %)	29	NR
Ades [6]	76	70 (33–85)	II	AZA 75 mg/m^2 days 1–5 or 1–7; cycle=28 days	CR, 17 % PR, 1 % Marrow CR, 8 % HI, 17 % ORR, 43 %	NR	29	31 % after 1.2 years from azacitidine initiation
Wong [71]	11	65 (42–80)	II	AZA 75 mg/m^2 days 1–7; cycle=28 days	CR, 9 % Marrow CR, 27 % PR, 9 % HI, 9 % ORR, 55 %	Local skin reactions (55 %), nausea (36 %), infection (73 %)	17	18 %
Fianchi [67]	31	69 (53–84)	II	AZA 50–75 mg/m^2 days 1–7 in 22 patients and 100 mg *flat* dose for 5–7 days in 9 patients	CR, 45 % PR, 3 % HI, 6 % ORR, 54 %	Grade 4: thrombocytopenia (6 %), anemia (6 %)	37	16 % after 12.7 months
Pleyer [90]	48	71 (38–87)	Matched pair analysis	AZA days 1–7 or 1, 5, 8, 9, or 1–5 or alternative; cycle=not specified	CR, 13 % PR, 6 % HI, 35 % ORR, 54 %	Grade 3/4: thrombocytopenia (44 %), neutropenia (21 %), anemia (40 %)	12.6	NR
Drummond [91]	32	70 (57–85)	II	AZA 75 mg/m^2 days 1–5, 8, 9; cycle=28 days	CR, 7 % PR 0 % Marrow CR, 7 %	Thrombocytopenia (46 %), neutropenia (40 %), infection 14 %, nausea 40 %	16	NR

DEC decitabine, *AZA* azacitidine, *IV* intravenous, *SQ* subcutaneously, *CR* complete remission, *HI* hematologic improvement, *PR* partial remission, *ORR* overall response rate, *NR* not reported

HSCT setting assessed 209 adult patients from 2001 to 2012 with a median age of 57 years and followed for a median of 51 months [84]. On multivariate analysis, CPSS score, Karnofsky performance status, and graft source were significant predictors of OS.

Conclusion

CMML is an MDS/MPN overlap syndrome, enriched with molecular abnormalities impairing epigenetic and chromatin regulation. Cytogenetic changes are seen in 20–30 % of patients, while molecular abnormalities are seen in ~90 %. Gene mutations involving *TET2* (60 %), *SRSF2* (50 %), *ASXL1* (40 %), and *RAS* (30 %) are common. Given the lack of formal treatment and response criteria, management is often extrapolated from MDS and MPN, with allogeneic HSCT being the only cure. Given the relatively poor responses to HMA, newer drugs exploiting the aforementioned molecular abnormalities are currently being explored, either in combination with HMA or as single-agent therapies. The developments of uniform response criteria and CMML-specific trials are much needed steps for this otherwise orphan disease.

Acknowledgments The authors would like to acknowledge the Henry J. Predolin Foundation for Research in Leukemia, Mayo Clinic, Rochester, MN.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Kristen McCullough and Dr. Mrinal Patnaik each declare no potential conflicts 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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