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Chronic Myelomonocytic Leukemia: 2018 Update on Diagnosis, Risk Stratification and Management

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Abstract

Disease Overview—Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disorder with overlapping features of myelodysplastic syndromes and myeloproliferative neoplasms, with an inherent risk for leukemic transformation (~15–20% over 3–5 years).

Diagnosis—Diagnosis is based on the presence of sustained (>3 months) peripheral blood monocytosis (≥1 x 10^9/L; monocytes ≥10%), along with bone marrow dysplasia. Clonal cytogenetic abnormalities occur in ~ 30% of patients, while >90% have gene mutations. Mutations involving *TET2* (~60%), *SRSF2* (~50%), *ASXL1* (~40%) and the oncogenic *RAS* pathway (~30%) are frequent; while the presence of *ASXL1* and *DNMT3A* mutations and the absence of *TET2* mutations negatively impact over-all survival.

Risk stratification—Molecularly integrated prognostic models include; the Groupe Français des Myélodysplasies (GFM), Mayo Molecular Model (MMM) and the CMML specific prognostic model (CPSS-Mol). Risk factors incorporated into the MMM include presence of nonsense or frameshift *ASXL1* mutations, absolute monocyte count>10 × 10^9/L, hemoglobin <10 gm/dl, platelet count <100 × 10^9/L and the presence of circulating immature myeloid cells. The MMM stratifies CMML patients into 4 groups; high (≥3 risk factors), intermediate-2 (2 risk factors), intermediate-1 (1 risk factor) and low (no risk factors), with median survivals of 16, 31, 59 and 97 months, respectively.

Risk-adapted therapy—Hypomethylating agents such as 5-azacitidine and decitabine are commonly used, with overall response rates of ~30–40% and complete remission rates of ~7–17%; with no impact on mutational allele burdens. Allogeneic stem cell transplant is the only potentially curative option, but is associated with significant morbidity and mortality.

Keywords

myelodysplastic syndrome; myeloproliferative neoplasm; chronic myelomonocytic leukemia; *ASXL1*; *TET2*

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DISEASE OVERVIEW

The 2016 iteration of the World Health Organization (WHO) classification of myeloid neoplasms defines chronic myelomonocytic leukemia (CMML) as a clonal hematopoietic stem cell disorder characterized by the presence of sustained (>3 months) peripheral blood (PB) monocytosis (≥1 x 10^9/L; monocytes ≥10% of white blood cell count) along with dysplastic features in the bone marrow (BM).[1] Secondary to the overlapping features of both, myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN), the classification of CMML as a unique myeloid neoplasm has undergone several changes dating back to the original French-American-British (FAB) co-operative group effort in 1982.[2] Due to renewed evidence demonstrating clinical, morphological and molecular differences, the 2016 WHO classification has once again recommended categorization of CMML into “proliferative” (MPN-CMML) and “dysplastic” (MDS-CMML) sub-types; based on a white blood cell count of ≥13 x 10^9/L for MPN-CMML.[1, 3] In addition, based on PB and BM blast %, CMML can be sub-classified into three categories; a) CMML-0 (<2% PB blasts including promonocytes and <5% BM blasts), b) CMML-1 (2–4% PB blasts including promonocytes and 5–9 % BM blasts), and c) CMML-2 (>5% PB blasts including promonocytes and 10–19% BM blasts and/or when any Auer rods are present).[1]

The median age at CMML diagnosis is ~71–74 years, with a male preponderance (1.5–3:1).[4–6] The exact incidence of CMML remains unknown, but is estimated at 4 cases per 100,000 persons per year.[7, 8] Therapy related CMML (t-CMML) cases have been described (~10% of all CMML), and like their MDS counterparts are associated with poor clinical outcomes.[9–11] Patients with t-CMML, in comparison to their *de novo* counterparts, are more likely to have cytogenetic abnormalities with higher risk karyotypic stratifications and shorter median over-all survivals (OS).[11] The presentation of patients with CMML is variable and the clinical heterogeneity is effectively captured by the current categorization into MDS-CMML and MPN-CMML.[12] Those with a MDS phenotype tend to present with peripheral blood cytopenias, effort intolerance, easy bruising, recurrent infections and transfusion dependance.[13] Those with a MPN phenotype tend to present with leukocytosis, monocytosis, hepatomegaly, splenomegaly and features of myeloproliferation such as; fatigue, night sweats, symptoms from organomegaly, bone pains, weight loss and cachexia.[13] Patients with MPN-CMML have a higher frequency of oncogenic *RAS* pathway mutations (*NRAS*, *KRAS, CBL* and *PTPN11*) and unique gene expression profiles.[3] Approximately 30% of CMML patients can present with antecedent or concomitant autoimmune diseases (rheumatoid arthritis, psoriasis, etc) and poorly defined systemic inflammatory syndromes.[14, 15] Rarely, CMML can present with leukemia cutis as an initial manifestation,[16] or directly present with blast phase disease.[17]

DIAGNOSIS

General Principles

An approach to patients with monocytosis is shown in Figure 1. It is important to exclude reactive causes of monocytosis before embarking on a workup of CMML. Monocytosis could be attributable to a number of non-malignant causes – infectious etiologies such as tuberculosis, chronic fungal infections, subacute bacterial endocarditis, viral and protozoal

infections (leishmaniasis); connective tissue disorders such as systemic lupus erythematosus and sarcoidosis, and lipid storage disorders. The recovery phase of an acute infection (usually viral) or bone marrow regeneration post chemotherapy is commonly associated with monocytosis.[18]

Once these etiologies have been ruled out, molecularly defined clonal hematopoietic disorders need to be considered. Firstly, chronic myeloid leukemia (CML) with the distinctive Philadelphia chromosome and the *BCR-ABL1* fusion oncogene must be evaluated and excluded.[19] Rearrangement of the platelet-derived growth factor receptors A (*PDGFRA*) and B (*PDGFRB*) should then be evaluated for. *PDGFRA* (chromosome *4q12*) and *PDGFRB* (chromosome *5q31–q32*) are type III receptor tyrosine kinases. Chromosomal translocations involving *PDGFRA/B* have been associated with myeloid neoplasms characterized by prominent eosinophilia and responsiveness to imatinib.[20, 21] At times, *PDGFR* rearranged myeloid neoplasms can present with monocytosis and BM dysplasia, but given their unique responsiveness to imatinib, these are no longer classified as CMML.[22] Patients presenting with a clinical phenotype of CMML with eosinophilia, should be assessed for t(5;12)(q31–q32;p13), giving rise to the *ETV6(TEL)-PDGFRB* fusion oncogene.[22] The association between monocytosis and *PDGFRA* rearrangements is uncommon.[23, 24] Additional molecular markers that should be assessed for, in the context of monocytosis and eosinophilia include *FGFR1* rearrangements and the *PCM1-JAK2* fusion.[25] Monocytosis can be associated with MPN such as primary myelofibrosis and polycythemia vera, where its presence adversely impacts survival.[26, 27] The presence of a prior well documented diagnosis of a MPN, or MPN-associated driver mutations such as *MPL* and *CALR*, make the diagnosis of CMML less likely.[1] Finally, the presence of bone marrow dysplasia in at least one hematopoietic lineage should be established. If myelodysplasia is absent or minimal, a diagnosis of CMML can still be made if clonal cytogenetic or molecular abnormalities are present (discussed below). Table 1 lists the 2016 WHO recommended diagnostic criteria for CMML.

Flow cytometry

Peripheral blood flow cytometry is a recent measure that has been used to help diagnose CMML.[28] Human monocytes can be divided into three subsets; $CD14^{+}/CD16^{-}$ (classical), $CD14^{+}/CD16^{+}$ (intermediate) and $CD14^{low}/CD16^{+}$ (non- classical), with different gene expression profiles, chemokine receptor expressions and phagocytic activities.[28, 29] The classical monocytes constitute majority of the human monocytes (~85%) in healthy conditions.[29] Compared to healthy donors and patients with reactive monocytosis, CMML patients demonstrate an increase in the fraction of classical monocytes ($CD14^{+}/CD16^{-}$) [cut off value 94%].[28] In the abovementioned French study, the associated specificity and sensitivity values were reported at 95.1% and 91.9% respectively.[28] Importantly, this repartition was noted to be independent of CMML mutational status and this increment corrected in CMML patients that responded to hypomethylating agents (HMA).[28] This technique has also been used to effectively distinguish monocytosis associated with CMML from monocytosis seen in patients with MPN,[30] and in identifying MDS patients with monocyte counts $<1 \times 10^{9}$/L who eventually develop CMML.[31] False negatives with this technique have been encountered in CMML patients with autoimmune diseases, where the

M02 fraction increases, resulting in a false decrease in the M01 fraction.[31] We hope that by using additional monocyte markers such as CCR2, CD36, HLA-DR and CD11c and better assessment techniques such as mass cytometry, we can improve upon the sensitivity and specificity of this assay.[32]

Histopathology and Immunohistochemistry

There is no single finding pathognomonic of the diagnosis of CMML. Bone marrow biopsies are often hypercellular with granulocytic hyperplasia and dysplasia. Monocytic proliferation can be present, but is often difficult to appreciate and immunohistochemical studies that aid in the identification of monocytes and their precursors is recommended.[33] Almost 80% of patients will demonstrate micro-megakaryocytes with abnormal nuclear contours and lobations, and 30% of patients can have an increase in BM reticulin fibrosis.[33] Twenty percent of patients can demonstrate nodules composed of mature plasmacytoid dendritic cells. The identification of promonocytes requires expertise and these cells are to be summated with blasts while estimating the blast count.[34]. Promonocytes are described as monocytic precursors that have a delicately convoluted, folded or grooved nucleus with finely dispersed chromatin, a small indistinct or absent nucleolus, and finely granulated cytoplasm (Figures two and three). [34, 35] On immunophenotyping the abnormal BM cells often express myelomonocytic antigens such as, CD13, CD33, with variable expression of CD14, CD68 and CD64. Markers of aberrant expression include CD2, CD15, CD56 or decreased expression of CD14, CD13, HLA-DR, CD64 or CD36. The presence of myeloblasts can be detected by expression of CD34. The most reliable markers on immunohistochemistry include CD68R and CD163. The monocytic cells are often positive for non-specific esterases and lysozyme, while the granulocytic precursors are often positive for lysozyme and chloroacetate esterase. This process can help differentiate CMML from other MPN such as CML and atypical CML, where BM monocytosis is uncommon.

The diagnostic criteria for CMML place a heavy onus on the presence of PB monocytosis (Figure three). As discussed, monocytosis is associated with a variety of reactive and clonal causes. Persistent reactive monocytosis with marrow dysplasia can wrongly be labelled as CMML. Similarly, CMML patients with progressive dysplasia or splenomegaly might develop peripheral blood cytopenias, and in spite of having monocytosis, fail to meet the diagnostic criteria for CMML. Bone marrow monocytosis can be seen in patients with underlying dysplasia and while these patients may eventually progress to CMML, at this point, BM monocytosis is not incorporated into the diagnostic algorithm.

Cytogenetic abnormalities in CMML

Clonal cytogenetic abnormalities are seen in ~20–30% of CMML patients.[5, 36–38] Common alterations include; trisomy 8, - Y, abnormalities of chromosome 7 (monosomy 7 and del7q), trisomy 21, and complex karyotypes.[37] The Spanish CMML specific cytogenetic risk stratification (CPSS) system categorizes patients in to 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.[37] Recently, in a large international study, 409 patients with CMML were analyzed for

cytogenetic and molecular abnormalities.[39] Thirty percent displayed an abnormal karyotype; with common abnormalities being, +8 (23%), −Y (20%), −7/7q-(14%), 20q-(8%), +21 (8%) and der(3q) (8%).[39] A step-wise survival analysis resulted in three distinct cytogenetic risk categories: high (complex and monosomal karyotypes), intermediate (all abnormalities not in the high or low risk groups) and low (normal, sole -Y and sole der (3q)) with median survivals of 3 (HR 8.1, 95% CI 4.6–14.2), 21 (HR 1.7, 95% CI 1.2–2.3) and 41 months, respectively (Mayo-French cytogenetic risk stratification system).[39]

Molecular abnormalities in CMML

There has been an exponential discovery of several molecular abnormalities in patients with CMML. On an average, patients with CMML demonstrate ~10–15 mutations per kilobase of coding DNA regions, similar to patients with acute myeloid leukemia (AML), but several folds lower than other malignancies such as melanoma and lung cancer.[40, 41] These mutations can broadly be divided into the following categories: (a) mutations in epigenetic control of transcription,[42–47] such as histone modification (*EZH2*, *ASXL1*, *UTX*), and DNA methylation (*TET2*, *DNMT3A, IDH1* and *IDH2*); (b) mutations in the spliceosome machinery (*SF3B1*, *SRSF2*, *U2AF1*, *ZRSR2, PRPF8*);[5] (c) mutations in genes that regulate cell signaling (*JAK2*, *KRAS*, *NRAS*, *CBL*, *PTPN11* and *FLT3*);[48–52] (d) mutations in transcription factors and nucleosome assembly (*RUNX1*, *SETBP1*);[49, 53, 54] and (e) mutations in DNA damage response genes such as *TP53* and *PHF6*.[55] The relative frequency of these mutations in individuals with CMML is shown in Table 2. Of these, mutations involving *TET2* (~60%), *SRSF2* (~50%), *ASXL1* (~40%) and the oncogenic *RAS* pathway (~30%) are most frequent, with only frame-shift and non-sense *ASXL1* mutations independently and adversely impacting OS.[44, 56]

The *ASXL1* gene (chromosome 20q11) regulates chromatin by interacting with the polycomb- group repressive complex proteins (PRC1 and PRC2).[42] In a seminal paper, Abdel-Wahab et al. demonstrated that *ASXL1* mutations resulted in loss of PRC2-mediated H3K27 (histone 3 lysine 27) tri-methylation.[57] In addition, Balasubramani et al. demonstrated that *ASXL1* truncations conferred enhanced activity on the ASXL1-BAP1 (BRCA associated protein 1) complex.[58] These interactions result in a global erasure of H2AK119Ub and depletion of H327Kme3, promoting dysregulated transcription and oncogenesis. *EZH2* mutations (chromosome 7q36.1) occur in <5% of CMML patients, and unlike in epithelial malignancies and lymphoproliferative disorders are loss-of-function mutations.[59] *EZH2* mutations in CMML almost always co-occur with *ASXL1* mutations, are frequently associated with a MPN-CMML phenotype, and while they themselves do not impact either OS or LFS, *ASXL1/EZH2* co-mutated patients have a shorter OS, in comparison to *ASXL1*mt patients alone.[59]

The *TET2* gene located on chromosome 4q24 is a member of the TET family of proteins.[60] TET2 has a dioxygenase enzymatic activity and converts 5-methyl-cytosine to 5-hydroxymethyl-cytosine (5hmC). 5hmC, represents a new base in genomic DNA, which may have a specific effect on transcription.[61, 62] Although *TET2* mutations are widely prevalent in CMML (~60%), they have not been shown to independently impact either OS or LFS.[44, 63] In a recent study, the presence of clonal *TET2* mutations, in the absence of

clonal *ASXL1* mutations (*ASXL1wt/TET2mut*), had a favorable impact on OS.[64] The reason for this association is unclear. In MDS and younger patients with CMML (age <65years), the presence of clonal *TET2* mutations, in the absence of clonal *ASXL1* mutations, has been associated with response to HMA.[65, 66]. Mutations involving *TET1, TET3* and *ASXL2* are extremely uncommon in CMML.[67]

DNA methylation is mediated by a family of DNA methyltransferase enzymes (DNMT), including DNMT1, DNMT3A (chromosome 2p23), and DNMT3B.[68] DNMT1 primarily maintains pre-existing DNA methylation patterns, whereas DNMT3A and DNMT3B carry out *de novo* DNA methylation.[68] *DNMT3A* mutations are seen in ~5% of CMML patients and independently and adversely impact both OS and LFS.[69] Of note, a recurrent Arginine882 (R882) hot spot accounts for 40–60% of *DNMT3A* mutations, with limited data suggesting loss of methyltransferase activity in *in vitro* assays.

Spliceosome component mutations (*SRSF2, SF3B1, U2AF1, PRPF8* and *ZRSR2*) affect pre-mRNA splicing.[5] *SRSF2* mutations are common in CMML (~50%) and are associated with increasing age, less pronounced anemia and a diploid karyotype.[5] Thus far, *SRSF2* mutations have not demonstrated an independent prognostic impact on both, OS and LFS.[5, 44, 70] *SF3B1* mutations have a high prevalence (~80%) in patients with MDS and ring sideroblasts (RS)[71] and can also be seen in patients with CMML and RS (~10%).[5] These mutations do not influence either the OS or LFS.[72, 73] Similarly, *U2AF1* and *ZRSR2* mutations are seen in ~10% of CMML patients and have thus far lacked an independent prognostic effect.[74]

Common signal pathway mutations in CMML include; oncogenic *RAS* pathway mutations (~30%, *NRAS, KRAS, CBL* and *PTPN11*), and *JAK2*V617F (~10%).[44, 49] *RAS* pathway mutations are associated with a MPN-like phenotype.[75] Although univariate analysis studies with *RAS* mutations have demonstrated inferior outcomes in CMML, these findings have not been substantiated in multivariable models.[36, 44] 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.[44, 49] *RUNX1* is essential for normal hematopoiesis and mutations can be seen in ~10–15% of patients with CMML.[44, 49] Although these mutations do not impact OS, there is a trend towards a higher risk for AML progression.[76]

The sequence of genetic events leading to the clinical phenotype of CMML remains under investigation. It is thought that the initial driver mutation is likely to be a mutation in *TET2* or *ASXL1*. This assumption is based on the high frequency of these mutations (~40–60%) in CMML,[77, 78] and results of single-cell tracking experiments.[79] Secondary mutations in the spliceosome machinery (such as in *SRSF2*) and cytokine signaling (*NRAS* or *CBL*) may allow a subset of these clones to progress, resulting in the typical phenotype associated with this disease.[55, 80] A recent paper has demonstrated that concurrent *Tet2* loss and *Nras*G12D expression in hematopoietic cells induced myeloid transformation, with a fully penetrant CMML phenotype in mice.[81]

RISK STRATIFICATION

Numerous prognostic models have been developed for CMML. In this regard, the value of Bournemouth, Lille, International Prognostic Scoring Systems (IPSS) and the revised-IPSSS is limited, as they were designed primarily for patients with MDS, excluding CMML patients with a MPN phenotype.[82, 83] The MD Anderson prognostic system (MDAPS) is CMML specific and identified a hemoglobin (HB) level <12 gm/dl, presence of PB immature myeloid cells (IMC), absolute lymphocyte count (ALC) >2.5 x 10^9/L and ≥ 10% BM blasts as independent predictors for inferior OS.[36] The MDAPS was subsequently applied to 212 CMML patients in the Dusseldorf registry[84]; in a univariate analysis circulating IMC had no prognostic impact, while on multivariable analysis, elevated lactate dehydrogenase, BM blast count >10%, male gender, HB <12 gm/dl and ALC >2.5 x 10^9/L were independently prognostic.[84]

The Global MDAPS (2008) was developed for patients with *de novo* MDS, secondary MDS and CMML (*n*=1,915).[85] Independent prognostic factors included; older age, poor performance status, thrombocytopenia, anemia, increased BM blasts, leukocytosis (>20 x 10^9/L), chromosome 7 or complex cytogenetic abnormalities and a prior history of red blood cell transfusions.[85] This model identified 4 prognostic groups with median survivals of 54 (low), 25 (intermediate-1), 14 (intermediate-2) and 6 months (high), respectively.[85] The CMML-specific prognostic scoring system (CPSS) identified 4 variables as being prognostic for both OS and LFS; FAB and WHO CMML-subtypes, red blood cell transfusion dependency, and the Spanish cytogenetic risk stratification system. [6, 37] One point was accorded for each variable, with the exception of high risk cytogenetics which earned 2 points, and four risk categories were determined: low (0 points), intermediate-1 (1), intermediate-2 (2–3), and high risk (4–5).[6]

The discovery of gene mutations in CMML has resulted in the development of molecular prognostic models. A Mayo Clinic study (n=226) analyzed several parameters, including *ASXL1* mutations; on multivariable analysis, risk factors for survival included HB <10 gm/dl, platelet count <100 × 10^9/L, AMC>10 × 10^9/L and circulating IMC.[86] *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.[86] The GFM demonstrated an adverse prognostic effect for *ASXL1* mutations in 312 patients with CMML; additional risk factors on multivariable analysis included age >65 years, WBC >15 × 10^9/L, platelet count <100 × 10^9/L and HB <10 gm/dl in females and <11 gm/dl in males.[44] The GFM model assigns 3 adverse points for WBC >15 × 10^9/L and 2 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.[44] It should be noted that all nucleotide variations (missense, nonsense and frameshift) were regarded as *ASXL1* mutations in the Mayo study,[86] whereas only nonsense and frameshift *ASXL1* mutations were considered in the French study[44].

To further clarify the prognostic relevance of *ASXL1* mutations, an international collaborative cohort of 466 CMML patients was analyzed.[39] In univariate analysis, survival was adversely affected by *ASXL1* (nonsense and frameshift) mutations. In multivariable analysis, *ASXL1* mutations, AMC >10 × 10^9/L, HB <10 gm/dl, platelets <100 × 10^9/L and circulating IMC were independently predictive of shortened OS. 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 (2 risk factors; HR 3.4, 95% CI 2.0–5.6) intermediate-1 (one risk factor; HR 1.9, 95% CI 1.1–3.3) and low (no risk factors) risk categories with median survivals of 16, 31, 59 and 97 months, respectively.[56] This model is referred to as the Mayo Molecular Model. Recently the CPSS model was updated to include molecular abnormalities including *ASXL1, RUNX1, NRAS* and *SETBP1* mutations (CPSS-Mol).[87] These mutations, in addition to the prior CPSS cytogenetic scores were used to calculate the CPSS genetic score. One point each was assigned for an intermediate-1 genetic score, WBC ≥ 13 x 10^9/L, BM blasts≥ 5% and red blood cell transfusion dependancy, 2 points for intermediate-2 genetic score and 3 points for a high risk genetic score.[87] The CPSS-Mol stratified CMML patients into four risk categories, low (0 risk factors), intermediate-1(1 risk factor), intermediate-2 (2–3 risk factors) and high (≥4 risk factors) risk, with median OS of not reached, 64, 37 and 18 months; with respective 4-year leukemic transformation rates of 0%,3%, 21% and 48%.[87] Table 3 highlights the CMML specific prognostic models along with their relevant components.

Seven clinical prognostic models, not incorporating *ASXL1* mutational status (IPSS, R-IPSS, MDAPS, Global MDAPS, Dusseldorf, CPSS and Mayo model) were statistically compared in a large dataset of CMML patients (n=1832).[82] All seven models were found to be valid with comparable performance, but were vulnerable to upstaging.[82]

Rates of leukemic transformation vary among different series of CMML patients reported in the literature. However, most studies quote an incidence of 15–20%.[88–90] In a study of 274 CMML patients followed for a median of 17.1 months, blast transformation (BT) occurred in 36 (13%).[17] On multivariable analysis, risk factors for BT were presence of PB blasts (HR 5.7; 95% CI 2.8–11.9) and female gender (HR 2.6; 95% CI 1.3–5.1); and the results remained unchanged when analysis was restricted to CMML-1. *ASXL1/SRSF2/SETBP1* mutational frequencies were not significantly different between time of CMML diagnosis and BT. Median survival post-BT was 4.7 months (5-year survival 6%) and was better with allogeneic stem cell transplant (HCT) (14.3 months vs. 4.3 months for chemotherapy vs. 0.9 months for supportive care; P = 0.03).[17]

RISK ADAPTED THERAPY

After its inclusion as a specific category of myeloid neoplasms in the 2008 WHO classification, treatment options for CMML have evolved. In the late 1990's, major treatment options consisted of chemotherapy such as etoposide, cytarabine, *all-trans* retinoic acid,[91–93] topotecan,[94],[95] 9-nitro-campothecin (topoisomerase inhibitor),[96] and lonafarnib (farnesyltransferase inhibitor).[97] Collectively, response rates in these trials were disappointing and therapy was associated with significant toxicities.

The United States Food and Drug Administration (FDA) approved two HMA, 5-azacitidine and decitabine, for treatment of patients with MDS. Two pivotal randomized studies that established the efficacy and safety of these drugs included a total of 361 patients with MDS.[98, 99] However, these studies only had 14 patients with CMML each, and the response rates for patients with CMML were not reported separately. Since the publication of these studies, several Phase II studies have reported the outcomes of patients with CMML who were treated with HMA.[73, 100–107] A complete list of the studies, including the dose and schedule of the drugs used, toxicities, response rates and survival are shown in Table 4. The overall response rate ranged from 25–70% (~30–40%), and median OS ranged from 12 to 37 months. Braun et al showed that mutations in *ASXL1*, *NRAS*, *KRAS*, *CBL*, *FLT3*, and *JAK2* genes, and hypermethylation of the promoter of the tumor suppressor gene - transcription-intermediary factor-1 gene (TIF1γ) did not predict response or survival in 39 CMML patients treated with decitabine. However, lower *CJUN* and *CMYB* gene expression levels independently predicted improved OS. There was a trend towards higher response rate in patients with a *TET2* mutation (when not associated with an *ASXL1* mutation), although it did not reach statistical significance.[101] On multivariable analysis, Ades et al showed that bone marrow blasts >10% and WBC>13 x 10^9/L had a prognostic impact on OS among 76 patients treated with azacitidine.[100] Fianchi et al showed that improved OS was associated with an absolute monocyte count <10 x 10^9/L, and PB blasts <5% at the start of therapy with HMA.[103] Pleyer et al conducted a matched-pair analysis of CMML patients treated with azacitidine (n=42) versus those who were treated with best supportive care (BSC, n=42) or with hydroxyurea (n=22). Although there was an improvement in median OS in the azacitidine arm (31 months) compared to BSC (17 months), these results were not statistically different (p=0.25), possibly due to the small sample size. Similarly, there was no difference in median OS between the azacitidine and hydroxyurea treatment arms (7.5 vs. 6.2 months, respectively, p=0.22). Next generation sequencing studies of CMML patients treated with HMA have shown that these agents do not alter the mutational allele burdens, even in responding patients.[40] Hematological responses obtained are often not durable, and are associated with significant changes in DNA methylation arguing for an epigenetic restoration of normal hematopoiesis, without significantly altering disease biology or progression to AML.[40]

A recent phase I clinical trial (n=20) has demonstrated safety and potential efficacy (35% MDS international working group (IWG) and spleen response) with ruxolitinib (JAK inhibitor), in patients with CMML.[108] This trial has currently been expanded to a phase II design and is currently accruing. Additional JAK/STAT inhibitors being preclinically assessed include momelotinib and pacritinib.[109] Given the inherent, demonstrable, GM-CSF (granulocyte-macrophage colony stimulating factor) dependant pSTAT5 (phosphorylated Signal Transducer and Activator of Transcription 5) sensitivity in CMML patients, targeted anti-GM-CSF monoclonal antibody therapy (lenzilumab) is being developed (NCT02546284-www.clinicaltrials.gov).[110] Tipifarnib a farnesyl transferase inhibitor (NCT02807272) and SL-401 a recombinant fusion protein composed of the catalytic and translocation domains of diphtheria toxin (DT) fused via a Met-His linker to IL3.11 (NCT02268253), are also undergoing clinical trial assessments in patients with CMML.

Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation 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), non-relapse mortality and post-transplant disease relapse. There unfortunately exists no prospective data analyzing the risks and benefits for HCT in CMML. The response rates in retrospective studies have ranged from 17% to 50%, with corresponding treatment related mortality rates ranging from 12% to 52% (Table 5).[111–118] The ten-year OS of 85 patients who underwent HCT at Fred Hutchinson Cancer Center was 40%. A multivariable model identified increasing age, higher HCT comorbidity index and poor-risk cytogenetics to be associated with increased mortality and reduced relapse-free survival (RFS).[111] The European Group for Blood and Marrow Transplantation reported an OS of 42% for 283 patients with CMML that underwent HCT. 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.[117] A recent application of the CPSS in the HCT setting, assessed 209 adult patients from 2001 to 2012 with a median age of 57 years and followed for a median of 51 months.[7] On multivariate analysis, CPSS score, Karnofsky performance status and graft source were significant predictors of OS.

In general, for younger patients with higher risk disease and an acceptable co-morbidity index, allogeneic HCT is the preferred treatment modality.[65] With the advent of reduced intensity conditioning and alternate donor sources (haploidentical HCT and double umbilical cord blood units), an increasing number of patients have access to HCT. While reduced intensity conditioning is associated with lower non-relapse mortality, disease relapse rates are higher in comparison to myeloablative regimens.[119, 120] Similar to MDS, cytoreductive therapy or HMA are often considered prior to HCT in patients with increased BM blasts (CMML-2) or prior to a reduced intensity conditioning.[121] A recent retrospective study (n=83) demonstrated prior therapy with HMA followed by allogeneic HCT was associated with a lower cumulative incidence of relapse (22% versus 35%; p=0.03), without a significant increase in the one-year transplant related mortality.[122] This finding needs prospective validation.

Recommendations: Hydroxyurea remains the cornerstone of therapy for patients with myeloproliferative features. Guidelines for supportive care measures such as the use of erythropoietin analogs for the treatment of anemia, prophylactic antibiotics for isolated neutropenia and iron chelation therapy for patients with a heavy transfusion burden are in general similar to patients with MDS, and data for their use specifically in patients with CMML do not exist. Standard induction chemotherapy should be considered for all eligible patients who develop blast transformation. Hypomethylating agents remain the most commonly used therapeutic intervention for patients with CMML. The presence of an elevated WBC count (>13x10^9/L), palpable splenomegaly and increased bone marrow blast percentage (>10%) are all associated with a worse survival while on therapy with hypomethylating agents. Although several novel mutations (such as ASXL1, RUNX1, NRAS and SETBP1) have been described to adversely affect survival of untreated CMML

patients, their impact on patients undergoing therapy with hypomethylating agents is unclear at this time. Unfortunately, the response rates and survival following therapy is suboptimal, and therefore clinical trial participation is strongly encouraged.

The role of allogeneic HCT in CMML remains controversial. Similar to MDS, younger patients with an adverse survival, as determined by newer prognostic models incorporating molecular aberrations, should be considered for HCT. Older patients with a high HCT comorbidity index do not benefit from HCT, and are best suited for clinical trials.

CONCLUSION

CMML, a myeloid neoplasm with features of MDS and MPN, often presents with PB monocytosis and has an inherent risk for transformation to AML. Clonal cytogenetic changes are seen in ~30% of patients and the CPSS and Mayo French Cytogenetic systems effectively risk stratify CMML patients based on cytogenetic abnormalities. Gene mutations are seen in >90% of patients, with common abnormalities involving; epigenetic regulators (*TET2*~60% and *ASXL1*~40%), spliceosome components (*SRSF2*~50%) and cell signaling (oncogenic *RAS*~30%). Of these, only frame-shift and nonsense *ASXL1* mutations have universally been shown to negatively impact OS. Lower risk, CMML patients that present with MPN-like features are effectively managed with hydroxyurea. Hypomethylating agents are associated with overall response rates of ~ 30–40%, with complete remission rates of ~ 15%. These responses are generally not sustained, do not alter mutational allele burdens, and survival after loss of response is often dismal. Allogeneic HCT remains the treatment of choice for younger patients with higher risk disease. Complications of HCT including, non-relapse mortality, acute and chronic graft versus host disease, limit generalized applicability of this treatment strategy. The development of CMML specific disease response criteria and clinical trials exploiting the genetic and epigenetic abnormalities in CMML, are important milestones to look forward to.[123]

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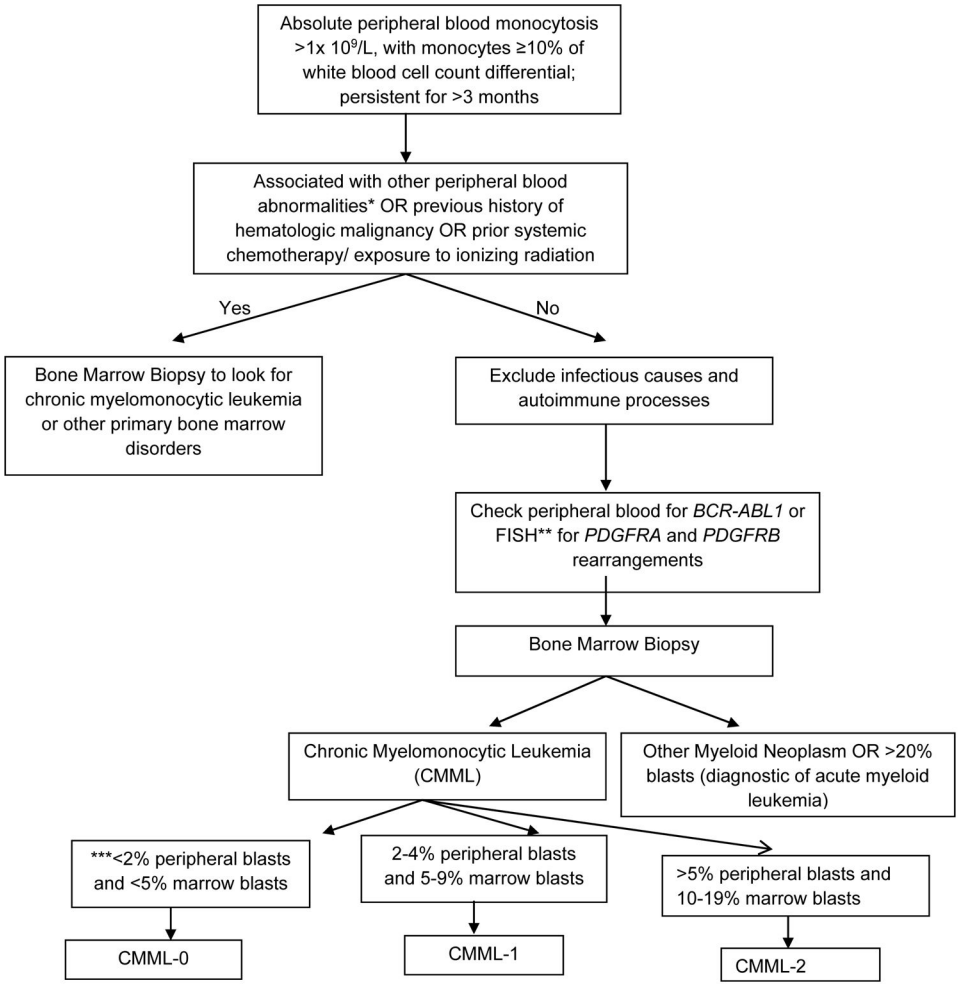

Figure 1.

A Schematic approach to the differential diagnosis of peripheral blood monocytosis.

*: Peripheral blood abnormalities include unexplained anemia, thrombocytopenia, thrombocytosis, leukocytosis, eosinophilia, granulocytic dysplasia (pseudo Pelger Huët cells), circulating immature myeloid cells such as myelocytes, metamyelocytes and promyelocytes, promonocytes and blasts.

**: FISH – fluorescence *in-situ* hybridization, *PDGFRA* and *PDGFRB*: Platelet-derived growth factor – A and Platelet-derived growth factor – B.

FISH testing for *PDGFRA* and *PDGFRB* rearrangements is highly recommended if the peripheral blood monocytosis is associated with concomitant eosinophilia. The *ETV6-PDGFRB* fusion oncogene can give rise to clonal monocytosis mimicking CMML, but is in fact a unique molecularly defined myeloid neoplasm (not to be diagnosed as CMML). Similarly *PDGFRA* fusions are commonly associated with eosinophilia, but rarely can have associated monocytosis. Most *PDGFRA* fusions occur due to the karyotypically occult CHIC2 deletion (not detectable by metaphase cytogenetics) resulting in the *FIP1L1-PDGFRA* fusion oncogene. The World Health Organization also mandates FISH testing for *FGFR1* rearrangements and the *PCM1-JAK2* fusion, however, these abnormalities are very uncommonly associated with monocytosis.

*** While estimating peripheral blood blasts in a patient with CMML, the blasts have to be summated with circulating promonocytes.

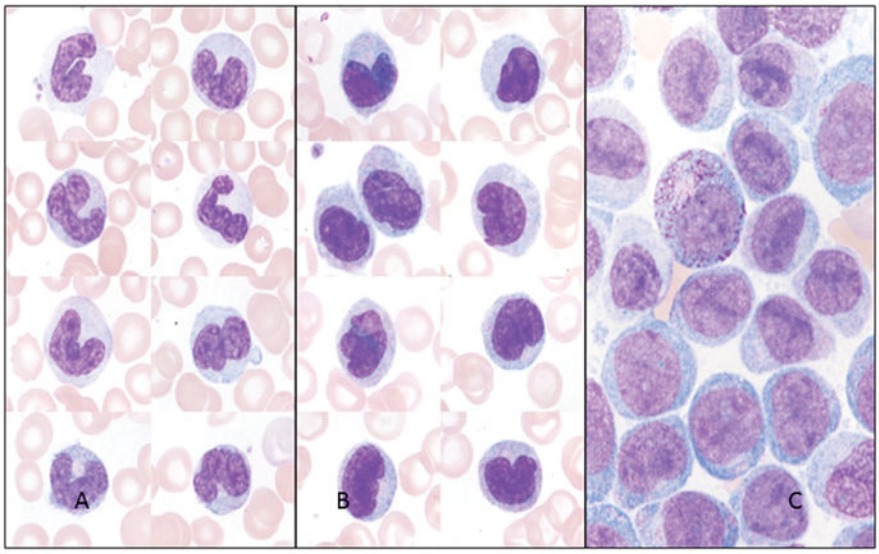

Figure Two.

A. Peripheral blood smear demonstrating monocytes with well-defined nuclear lobes and mature chromatin. Wright-Giemsa 1000 X magnification.

B. Peripheral blood smear demonstrating promonocytes with open chromatin, nuclear folds and less defined nuclear lobes. Wright-Giemsa 1000 X magnification.

C. Bone marrow aspirate demonstrating monoblasts with open chromatin, lack of nuclear lobes and variable nucleoli. Wright-Giemsa 1000 X magnification.

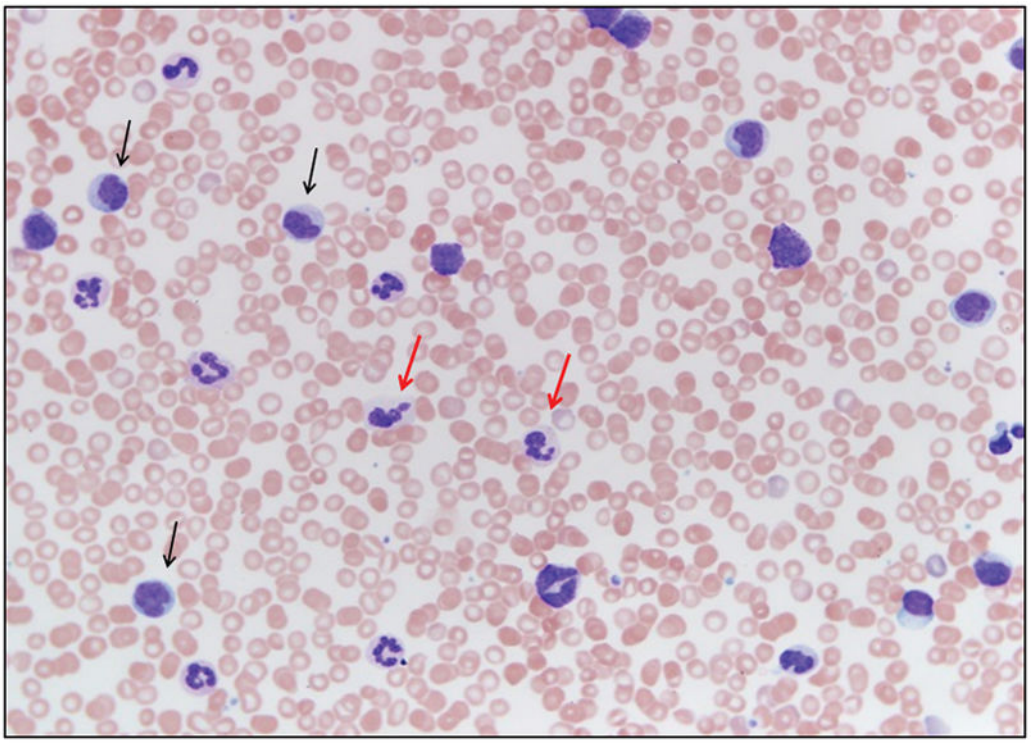

Figure Three.

Peripheral blood smear of a patient with chronic myelomonocytic leukemia demonstrating circulating promonocytes (black arrows) and dysplastic granulocytes (red arrows). Wright-Giemsa 100 X magnification.

Table 1

2016 World Health Organization (WHO) recommended diagnostic criteria for chronic myelomonocytic leukemia (CMML)

1	Presence of persistent (>3 months) peripheral blood monocytosis > 1 x10^9/L, with monocytes constituting ≥10% of the white blood cell count differential.
2	Not meeting WHO criteria for *BCR-ABL1* driven chronic myeloid leukemia, essential thrombocythemia, polycythemia vera or primary myelofibrosis *.
3	No evidence for *PDGFRA* or *PDGFRB* rearrangements, and the absence of *FGFR1* rearrangements or the *PCM1-JAK2* fusion in the context of concomitant eosinophilia **.
4	< 20% blasts/blasts equivalent (promonocytes, monoblasts and myeloblasts) in the peripheral blood and bone marrow.
5	Dysplasia in one or more myeloid cell lineages. If myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if the other requirements are met and (see point 6)
6	An acquired clonal cytogenetic or molecular genetic abnormality (*TET2, ASXL1, SRSF2 and SETBP1*) is present in hemopoietic cells ***.

* Myeloproliferative neoplasms (MPN) such as primary myelofibrosis and polycythemia vera can present with concurrent monocytosis. A previous documented history of MPN excludes a diagnosis of CMML. In addition, the presence of MPN like features in the bone marrow, or the presence of MPN-associated driver mutations, especially *MPL* and *CALR* make the diagnosis of CMML unlikely.

** *PDGFRA* abnormalities most often involve the cryptic *CHIC2* deletion at chromosome 4q12, resulting in the *FIP1L1-PDGFRA* fusion, commonly associated with peripheral blood eosinophilia and increased bone marrow mast cells.

PDGFRB abnormalities most often involve the *ETV6-PDGFRB* gene fusion with ~25 additional reported partners. This fusion is associated with peripheral blood monocytosis and concomitant eosinophilia.

FGFR1 rearrangements often result in an aggressive stem cell leukemia/lymphoma syndrome characterized by MPN, eosinophilia and the development of T cell-acute lymphoblastic leukemia (ALL).

The *PCM1-JAK2* fusion usually results in eosinophilia with T-ALL or B-ALL.

*** While gene mutations involving *TET2* (~60%), *SRSF2* (~50%), *ASXL1* (~40%) and *SETBP1* (~15%) are common in CMML, they are not specific for the disease. *TET2* and *ASXL1* mutations can also be detected in patients with normal blood counts as a part of age related clonal hematopoiesis (clonal hematopoiesis of indeterminate potential).

Table 2

Relative frequencies of somatic mutations in patients with chronic myelomonocytic leukemia

Major class of genetic mutation		Gene	Frequency of mutation
Epigenetic Control	Histone modification	*ASXL1**	40%
		EZH2	5%
	DNA methylation	*TET2*	60%
		*DNMT3A**	5%
	Dual effect	*IDH1*	1%
		IDH2	5–10%
Cell signaling		*JAK2*V617F	5–10%
		CBL	15%
		*NRAS**	15%
		KRAS	10%
		PTPN11	5%
		FLT3	<5%
Pre-mRNA splicing		*SRSF2*	50%
		SF3B1	5–10%
		U2AF1	5–10%
		ZRSR2	5%
Transcription and nucleosome assembly		*RUNX1**	15%
		*SETBP1**	15%
DNA damage		*TP53*	1%
		PHF6	5%

*Annotates genes that have been shown in various studies to have an independent and adverse prognostic impact on survival outcomes.

Table 3

Prognostic scoring systems for chronic myelomonocytic leukemia

Prognostic Score	Year	Number of Patients	External Validation	Variables included in the final model	Median Survival in months				Transformation into AML
					Low risk	Intermediate-1 risk	Intermediate-2 risk	High risk	
Onida et al[5] (MDAPS)	2002	213	No	1. Hemoglobin <12 gm/dL 2. Circulating immature myeloid cells 3. Absolute lymphocyte count >2.5 x 10^9/L 4. Bone marrow blasts >10%	24	15	8	5	19% developed AML after a median time of 7 months
Germing et al[4] (Dusseldorf score for CMML)	2004	288	No	1. Bone marrow blasts ≥5% 2. LDH >200 U/L 3. Hemoglobin ≤9 gm/dl 4. Platelets ≤100 x 10^9/L	93	26		11	8%, 23% and 23% at 5 years, respectively
Such et al[42] (CPSS Model)	2013	578	Yes, in 274 patients	1. CMML FAB type 2. CMML WHO type 3. CMML-specific cytogenetics 4. RBC transfusion dependence	72	31	13	5	Probability of AML evolution at 5 years, 13%, 29%, 60%, and 73%, respectively
Itzykson et al[22] (GFM Model)	2013	312	Yes, 165 patients	1. Age >65 years 2. WBC >15x10^9/L 3. Anemia 4. Platelets <100 x10^9/L	Not reached	38.5		14.4	AML-free survival was 56.0, 27.4, and 9.2 months, respectively

Prognostic Score	Year	Number of Patients	External Validation	Variables included in the final model	Median Survival in months				Transformation into AML
					Low risk	Intermediate-1 risk	Intermediate-2 risk	High risk	
				5. *ASXL1* mutation					
Patnaik et al[34] (Mayo Model)	2013	226	Yes, 268 patients	1. Increased absolute monocyte count >10×10^9/L 2. Presence of circulating blasts 3. Hemoglobin <10 gm/dL 4. Platelet count <100 $\times10^9$/L	32	18.5		10	NR
Patnaik et al (Mayo Molecular Model)	2014	466	No	1. Increased absolute monocyte count >10×10^9/L 2. Presence of circulating blasts 3. Hemoglobin <10 gm/dL 4. Platelet count <100 $\times10^9$/L 5. Frameshift and nonsense *ASXL1* mutations	97	59	31	16	At a median follow up of 23 months, 75 (16%) leukemic transformations occurred.
Elena et al (CPSS-Mol)	2016	214	260	1. Genetic risk groups as defined by *CPSS cytogenetic risk stratification and gene mutations involving *ASXL1*,	Not reached	64	37	18	48 months cumulative incidence of AML evolution; 0%, 3%, 21% and 48%, respectively.

Prognostic Score	Year	Number of Patients	External Validation	Variables included in the final model	Median Survival in months				Transformation into AML
					Low risk	Intermediate-1 risk	Intermediate-2 risk	High risk	
				NRAS, SETBP1 and *RUNX1.* 2. Bone marrow blasts ≥ 5%. 3. WBC count ≥ $13x10^9$/L 4. Red blood cell transfusion dependancy					

Key: MDAPS- MD Anderson Prognostic Scoring System, CPSS- CMML specific prognostic scoring system, CMML- chronic myelomonocytic leukemia, GFM- Groupe Francophone des Myélodysplasies, LDH- lactate dehydrogenase, FAB- French American British, WHO – World Health Organization, WBC- white blood cell count.

The CPSS-Mol used a genetic risk group stratification that assigned a score of 0 for low risk cytogenetics and absence of *ASXL1/NRAS/SETBP1/RUNX1* mutations, a score of 1 for intermediate risk cytogenetics and mutations involving *ASXL1/SETBP1* and *NRAS*, and a score of 2 for high risk cytogenetics and *RUNX1* mutations

Table 4

Use of hypomethylating agents in chronic myelomonocytic leukemia (CMML)

Reference	Number of patients	Median Age (years, range)	Phase of Study	Treatment Regimen	Response Rates	Toxicity	Median Survival	Progression to Acute Myeloid Leukemia
Aribi (2007)[59]	19	66 (44–82)	II	Decitabine 100 mg/m^2 per course in three different schedules, repeated every 4 weeks	CR: 58% HI: 11%	Myelosuppression associated complications: 8%	19 months	NR
Wijermans (2008)[65]	31	71 (53–81)	II	Decitabine 15 mg/m^2 over 4 hours IV three times per day on three consecutive days, with a total dose of 135 mg/m^2 per course, every 6 weeks	CR: 10% PR: 16% HI: 19%	Nausea, vomiting, pneumonia, mortality due to sepsis: 3%	15 months	NR
Costa (2010)[61]	38	70 (36–83)	II	Azacitidine 75 mg/m^2/day for 7 days or 100 mg/m^2/day for 5 days every 4 weeks	CR: 11% PR: 3% HI: 25%	Pneumonia, mortality due to sepsis: 3%	12 months	NR
Garcia-Manero (2011)[63]	41 (4 with CMML)	70 (31–91)	I	1 cycle of subcutaneous azacitidine 75 mg/m^2 on the first 7 days of cycle 1, followed by oral azacitidine daily,120 to 600 mg, on the first 7 days of each additional 28-day cycle	ORR: 35% in previously treated patients and 73% in previously untreated patients	diarrhea, nausea, vomiting, febrile neutropenia, fatigue	NR	NR
Braun (2011)[60]	39	71 (54–88)	II	Decitabine 20 mg/m^2 per day intravenously for 5 days every 28 days	CR: 10% PR: 20% HI: 8% ORR: 38%	Neutropenia and thrombocytopenia (36%), severe infection (20%)	18 months	NR
Thorpe (2012)[64]	10	66 (41–76)	II	Azacitidine 75 mg/m^2 for 7 days or azacitidine 100 mg/m^2 for 5 days every 28 days	CR: 20% HI: 40% ORR: 60%	Thrombocytopenia, pneumonia (20%)	29 months	NR
Ades (2013)[58]	76	70 (33–85)	II	Azacitidine 75 mg/m^2 for 5–7 days every 28 days	CR: 17% PR: 1% Marrow CR: 8% HI: 17% ORR: 43%	NR	29 months	31% after 1.2 years from azacitidine initiation
Wong (2013)[66]	11	65 (42–80)	II	Azacitidine 75 mg/m^2 for 7 days every 28 days	CR: 9% Marrow CR: 27% PR: 9% HI: 9% ORR: 55%	Local skin reactions (55%), nausea (36%), infection (73%)	17 months	18%
Fianchi (2013)[62]	31	69 (53–84)	II	Azacitidine 50–75 mg/m^2 for 7 days 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%), grade 4 anemia (6%)	37 months	16% after 12.7 months
Santini (2013)	44	71 (42–84)	II	Decitabine 20 mg/m^2 for 5 days, every 28 days	CR: 14% PR: 2% Marrow CR: 17% ORR: 33%	Severe infections (17%)	19 months	NR

Reference	Number of patients	Median Age (years, range)	Phase of Study	Treatment Regimen	Response Rates	Toxicity	Median Survival	Progression to Acute Myeloid Leukemia
Pleyer (2014)	48	71 (38–87)	II	Azacitidine 75 mg/m^2 for 7 days in 42 patients, and 100 mg flat dose for 5–7 days in 6 patients	CR/marrow CR: 13% HI: 50% ORR: 54%	Grade 3–4 cardiac events (21%)	12.6 months	4% after 9 months
Drummond (2014)	32	70 (57–85)	II	Azacitidine 75 mg/m^2 for 7 days, every 28 days	CR: 7% PR: 0 Marrow CR: 7% HI:3% ORR: 17%	NR	16 months	33% after 13 months
Sekeres (2017)	53 with CMML	70 (28–93)	Randomized phase II	Azacitidine (75 mg/m2/day on days 1 to 7 of a 28–day cycle); Azacitidine plus lenalidomide (10 mg/day on days 1 to 21); or Azacitidine plus vorinostat (300 mg twice daily on days 3 to 9).	ORR: 38% (68% in the azacitidine and lenalidomide arm)	Azacitidine plus lenalidomide associated with higher incidence of skin rashes, while azacitidine and vorinostat with a higher incidence of Gastrointestinal side effects	Not reached	NR
Santini (2018)	43	71.5 (42–84)	II	Decitabine 20 mg/m^2 for 5 days, every 28 days	CR: 16% PR: 2.4% Marrow CR: 19% HI: 9.5% ORR: 47.6%	Thrombocytopenia (64%) Anemia (52%) Gastrointestinal side effects (23.8%)	17 months	57.5%after 51.5 months

Abbreviations Used:

CR: complete remission; PR: partial remission; HI: hematologic improvement; ORR: overall response rate; NR: not reported; CMML: chronic myelomonocytic leukemia.

Table 5

Summary of select allogeneic stem cell transplant studies for chronic myelomonocytic leukemia (CMML)

Reference	N	Age, yrs (median)	Disease Stage	Cytogenetics	Donor Type and Stem Cell Source	Conditioning (Myeloablative, reduced intensity)	Relapse rate and Treatment-related mortality	Outcomes
Kroger (2002)	50	44 (19–61)	CMML-1: 28 CMML-2: 17 Unknown: 5	Diploid: 18 Abnormal: 11 Unknown: 21	MRD: 43 MUD: 7 BM: 40 PBSC: 9	MAC: 50 RIC: 0	RR: 28% TRM: 52%	5-year OS: 21% 5-year DFS: 18%
Mittal (2004)	8	51 (20–64)	NR	Diploid: 3 Abnormal: 4 Unknown: 1	MRD: 6 MUD: 2 BM: 4 PBSC: 4	MAC: 4 RIC: 4	RR: 50% TRM: 12%	18 month OS: 35% 18 month DFS: 31%
Elliott (2006)	17	50 (20–60)	NR	Diploid: 9 Abnormal: 8	MRD:14 MUD:3 BM: 8 PBSC: 7	MAC: 16 RIC: 1	RR: 41% TRM: 41%	3 year OS: 18% 3-year RFS: 18%
Ocheni (2009)	12	56 (38–67)	CMML-1: 7 CMML-2: 3 Unknown: 2	Diploid: 7 Abnormal: 4 Unknown: 1	MUD: 11 MRD: 1 BM: 0 PBSC: 12	MAC: 7 RIC: 6	RR: 17% TRM: 25%	2-year OS: 75% 2-year DFS: 67%
Krishnamurthy (2010)	18	54 (38–66)	CMML-1: 8 CMML-2: 10	Diploid: 7 Abnormal: 11	MRD: 10 MUD: 8 BM: 6 PBSC: 12	MAC: 1 RIC: 17	RR: 44% TRM: 31%	3-year OS: 31% 3-year DFS: 47% (< 5% blasts) 3-year DFS: 20% (>5 % blasts)
Symeonidis (2010)	283	50 (NR)	CMML-MDS:45 CMML-MPN:60 Unknown: 178	NR	MRD: 160 MUD: 85 Unknown: 38 BM: 108 PBSC: 175	MAC: 152 RIC: 87	RR: 25% TRM: 37%	OS: 42% DFS: 38% (time interval not specified)
Eissa (2011)	85	51 (1–69)	CMML-1: 57 CMML-2: 26	Good: 45 Intermediate: 14 Poor: 22	MRD: 38 MUD: 47 BM: 32 PBSC: 53	MAC: 58 RIC: 27	RR (10 yrs): 27% TRM (10 yrs): 35%	10-year OS: 40% 10-year DFS: 40%
Park (2013)	73	53 (27–66)	CMML-1: 40 CMML-2: 29	Good: 48 Intermediate: 13 Poor: 9	MRD: 41 MUD: 32 BM: 27 PBSC: 46	MAC: 30 RIC: 43	RR (3 yrs): 35%	3-year OS: 32% 3-year DFS: 29%
Itonaga (2013)	141	49 (NR)	NR	NR	MRD: 68 MUD: 53 Cord: 10	MAC: 101 RIC: 40	NR	3-year OS: 47%

Reference	N	Age, yrs (median)	Disease Stage	Cytogenetics	Donor Type and Stem Cell Source	Conditioning (Myeloablative, reduced intensity)	Relapse rate and Treatment-related mortality	Outcomes
Duong (2015)	209	57 (23–74)	CPSS low/ intermediate-1– 88 (42%) Intermediate-2/high- 79 (38%) Missing- 42	CPSS Cytogenetic groups Low- 50% Intermediate-19% High- 17% Missing- 14%	MRD: 35% MUD: 45% MMUD: 19% BM: 16% PBSC: 84%	MAC: 51% RIC: 41% NMA: 5%	NR	OS at 1, 3 and 5 years for CPSS low / intermediate-1: 61%, 48%, 41%. Intermediate-2/high- 38%, 32%, 19%
Symeonidis (2015)	513	53 (18.5–75.4)	CMML-MDS:73 CMML-MPN: 110 CMML-1: 87 CMML-2: 32 Secondary AML- 95	Normal- 104 Abnormal- 60	MRD: 285 MUD: 228 BM: 119 PBSC: 394	MAC- 249 RIC- 226	RR (4yrs): 32% NRM (4yrs): 41%	4-year OS: 33% 4-year DFS: 27%
Liu HD (2017)	209	57 (23–74)	CMML-1: 140 (67%) CMML-2: 52 (25%) Missing: 17 (8)	NR	MRD: 73 MUD: 95 MMUD: 36	MAC: 105 RIC: 99 Missing: 5	RR (1,3 and 5 yrs.): 46%, 50% and 52% TRM (1,3 and 5 years): 19%, 23% and 28%	OS at 1,3 and 5 years: 50%, 38% and 30%.

Abbreviations Used:

N: total number of patients, yrs: years, CMML-1: chronic myelomonocytic leukemia-1, CMML-2: chronic myelomonocytic leukemia-2, AML- acute myeloid leukemia, CMML-MDS: chronic myelomonocytic leukemia-myelodysplasia type, CMML-MPN: chronic myelomonocytic leukemia- myeloproliferative type, MRD: matched related donor, MUD: matched unrelated donor, MMUD: mismatched unrelated donor, BM: bone marrow donor, PBSC: peripheral blood stem cell donor, MAC: myeloablative conditioning, RIC: reduced intensity conditioning, NMA: non myeloablative, RR: relapse rate, TRM: treatment-related mortality, NRM: non relapse mortality, OS: overall survival, DFS: disease-free survival; NR: not reported, CPSS- CMML specific prognostic scoring system.