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Review Article

Chronic Myelomonocytic Leukemia (CMML): A systematic Review of Literature and Update

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Abstract

Chronic Myelomonocytic Leukemia (CMML) is a hematologic malignancy classified as an overlapping Myelodysplastic Syndrome/Myeloproliferative Neoplasm (MDS/MPN) that can transform into Acute Myelogenous Leukemia (AML) with poor outcomes. CMML has distinctive biologic characteristics that may warrant new therapeutic approaches separate from MDS/MPN. There are limited effective therapies for this disease to prevent progression or transformation into AML, and outcomes are often dismal without allogeneic transplantation, especially in patients with high risk disease. As the genomic landscape of CMML continues to unravel and our prognostic scoring systems improve, individualized treatment approaches considering the entirety of this information will follow. We reviewed the literature on the current diagnostic criteria, subtypes of disease, common cytogenetic/molecular

aberrations, scoring systems, current treatment and future directions of therapeutic intervention.

Keywords: CMML; Chronic myelomonocytic leukemia; MPN; MDS; MDS/MPN overlap

1. Introduction

In 2008, World Health Organization (WHO)-appointed experts replaced the historical term `myeloproliferative disorders' (MPD) with the term `Myeloproliferative Neoplasm' (MPN) in alignment with the enhanced knowledge about the molecular biology of these diseases. The 2016 edition of the WHO-classification recognizes MPNs to comprise of several subtypes: Chronic Myeloid Leukemia (CML), Polycythemia Vera (PV), Essential Thrombocythemia (ET), Primary Myelofibrosis (PMF) and several 'atypical' subtypes, which include Chronic Neutrophilic Leukemia (CNL), Chronic Eosinophilic Leukemia, not otherwise specified (CEL), and Myeloproliferative Neoplasm, Unclassifiable (MPN-U) [1]. An important tenet of the 2016 WHO-classification is that in myelodysplastic syndrome (MDS)/MPN, the dysplastic and proliferative features must be present at the time of initial diagnosis, with the sole exception of MDS/MPN with Ring Sideroblasts (RS) and thrombocytosis. Patients with other subtypes, including Chronic Myelomonocytic Leukemia (CMML), may present in earlier phases in which the full disease phenotype has not fully developed. Indeed, a recent publication has proposed broadening the category of CMML to encompass variants in which monocytosis develops after a prior diagnosis of a myeloid malignancy, a category which is not included in the 2016 WHO classification [2] The MDS/MPN subtypes are typically identified by the type of myeloid subset that predominates in the Peripheral Blood (PB). For example, CMML and Juvenile Myelomonocytic Leukemia (JMML) are characterized by a unique expansion of peripheral blood monocytes, while atypical CML is associated with highly dysplastic granulocyte predominance. Multiparameter flow cytometry helps to characterize patients with CMML who have a specific expansion of 'classical' monocytes ($CD14^{hi}$/CD16neg), albeit with varying degrees of differentiation and proliferation which, in turn, result in the remarkable clinical heterogeneity. The genetic landscape is relatively homogeneous with well-defined mutations (ASXL1, NRAS, RUNX1, TET2, SRSF2, and SETBP1) which exert a prognostic impact on the patients [2, 3].

A recent study suggests that once CML, JMML, and the JAK2/MPL/CALR-associated MPNs are excluded, many of the chronic myeloid malignancies appear to share genetic and epigenetic features and it is possible that they should be considered collectively for risk stratification, treatment, and clinical studies [4]. The annual incidence of CMML is estimated at 1,100 cases per year in the United States (US), with a median age of 70 years and a male predominance. The diagnosis of CMML requires persistent (> 3 months) PB monocytosis (> $lx10^9$/L) with monocytes accounting for >10% of White Blood Cells (WBC) and bone marrow dysplasia. Recurrent somatic mutations are noted in > 90% of the patients and clonal cytogenetic abnormalities in > 30%. Clinical presentation may include cytopenias, dysplastic features of WBC, excess blasts, or proliferative features such as high WBC count (> 13 $x10^9$/L) and splenomegaly; rarely skin and lymph node infiltration and serous membrane effusions can occur.

CMML is divided by the 2016 WHO diagnostic criteria into three groups based upon blast percentage:

- CMML-0 with < 2% blasts in PB and < 5% blasts in the bone marrow,
- CMML-1 with 2% to 4% blasts in PB and/or 5% to 9% blasts in bone marrow and
- CMML-2 with 5% to 19% blasts in PB and/or 10% to 19% in bone marrow, and/or presence of Auer rods.

The so-called 'proliferative type' CMML (P-CMML) (leukocyte count > 13 $x10^9$/L) and `dysplastic type' CMML (D-CMML) (< 13 $x10^9$/L) are distinguished solely by leukocyte count; however, mutational patterns may help distinguish the two types. For example, mutations involving the JAK2/RAS/MAPK signaling pathways tend to be more common in patients with the `proliferative type' CMML [5, 6]. Recently "Oligomonocytic type" CMML (OM-CMML) was described, meeting all diagnostic criteria of CMML, including monocytosis of more than 10% of white blood cells, however with lower absolute monocyte count of more than 0.5$x10^9$/L, representing an early stage of D-CMML. OM-CMML that evolves to CMML has showed shorter overall survival [7]. In a retrospective analysis, Roman, D et al showed OM-CMML has longer AML-free survival than D-CMML and P-CMML (P=0.001, and P<0.001, respectively) [8].

1.2. Pathologic Classification of CMML

The bone marrow will often be hypercellular with dysplastic myeloid cells and may involve monocytosis or increased promonocytes. There are often micro-megakaryocytes present and the marrow occasionally has increased reticulin fibrosis, and may demonstrate nodules of mature plasmacytoid dendritic cells [9]. Morphologically these monocytes may demonstrate an abnormal appearance with bizarre nuclei and cytoplasmic granules and in some cases, monocytes are dysplastic and immature, endowed with immunosuppressive properties, i.e., so-called para-myeloid cells. Immunohistochemistry is important to identify monocytes and their precursors, as promonocytes are ultimately considered as blasts when classifying CMML. Myelomonocytic antigens including CD13, CD33, CD68R and CD163 are important as well as aberrant expression of CD2, CD15, CD56 or decreased expression of CD14, CD13, HLA-DR, CD64, or CD36 [9]. Stains for certain esterases and lysozyme may help differentiate between monocytes and granulocytic precursors. Clonal cytogenetic abnormalities are found in approximately 20-30% of patients with CMML and often include trisomy 8, -Y, monosomy 7, del(7q), trisomy 21, del(20q), der(3q), rearrangements with a 12p breakpoint, and complex karyotypes; however, del(5q) is almost never found [10, 11]. A survival analysis reported by Wassie et al led to the cytogenetic risk classification with low risk being normal or isolated -Y, high risk being trisomy 8, abnormalities of chromosome 7 or complex karyotype, and intermediate, being other abnormalities. The median survival in the low, intermediate and high risk groups were 3, 20 and 41 months, respectively [12].

The most frequent molecular abnormalities seen in CMML involve mutations in TET2 (~60%), SRSF2 (~50%), ASXL1 (~40%) and the RAS pathway (~30%: NRAS, KRAS, CBL, and PTPN11) [9]. It has been postulated that CMML arises from a mutation in TET2 or ASXL1 given the high frequency of these mutations, with a secondary mutation in the spliceosome (SF3B1, SRSF2, ZRSF2,

U2AF1) or cytokine signaling pathways (NRAS, KRAS, CBL, JAK2, FLT3) leading to the development of CMML [9]. There are more frequently molecular aberrations in patients with CMML compared to cytogenetic changes, with 40-50% of CMML patients harboring a mutation in TET2, SRSF2 or ASXL1 [13]. A study by Palomo et al. describes the molecular landscape of subtypes of MPN/MDS, including 119 patients with CMML, who had ancestral TET2 mutations, 71% of the time commonly associated with biallelic TET2 (46%) and TET2-SRSF2 (45%) [14]. This study attempts to describe the clonal hierarchy based on Variant Allele Frequency (VAF) adjusted for copy number and zygosity. Founder mutations of ASXL1 and SRSF2 mutations were also seen in 49% and 55% of patients, respectively. ASXL1 and SRSF2 were preceded by a TET2 mutation in 9/119 and 14/119, respectively. Mutations in signaling genes (KRAS, NRAS, CBL and JAK2) were commonly found in secondary clones. RUNX1 mutations were found in 25% of patients either as ancestral or secondary, however they never preceded TET2 or SRSF2. Several studies have aimed to determine the prognostic implications of these mutations. ASXL1 mutations resulting in nonsense or frameshift mutations have been linked independently to worse overall survival (OS) [15]. Patients with concurrent ASXL1/EZH2 mutations have been shown to have shorter OS compared to patients with ASXL1 mutation [16]. TET2 mutations have not been shown to be independently prognostic, and in the absence of ASXL1 mutation, these patients had longer OS [17]. DNMT3A mutations are seen in approximately 5% of patients with CMML and have been shown to be associated with poor OS and Leukemia Free Survival (LFS) [18]. Spliceosome mutations including SRSF2, SF3B1, U2AF1 and ZRSR2 have not been shown to be independently prognostic. RAS pathway mutations that typically co-occur with mutations in ASXL1, TET2 and SRSF2 have been associated with MPN-like CMML, with shorter OS and LFS [19]. RUNX1 mutations are seen in approximately 10-15% of patients and are associated with earlier leukemic transformation [20].

1.2. Prognostic Scoring Systems in CMML

The International Prognostic Scoring Systems (IPSS) and the revised-IPSSS scores typically used for MDS excluded patients with MPN-like CMML, therefore limiting its use. Multiple prognostic scoring systems have since been proposed for CMML to better predict outcomes, which have been validated [21]. The global MDAPS was developed after analysis of 1915 patients with MDS – including those with MPN-like CMML, secondary MDS and MDS with prior therapy [22]. Independent prognostic factors after multivariate analysis included age, performance status, thrombocytopenia, anemia, BM blasts, leukocytosis (>20k), chromosome 7 or complex cytogenetics, and a history of red cell transfusions. Patients were then classified into four prognostic groups with median OS 54 months (low), 25 months (intermediate-1), 14 months (intermediate 2) and 6 months (high). Subsequently the CMML-specific prognostic scoring system (CPSS) was developed with the following variables associated with OS and leukemic transformation: FAB and WHO CMML subtypes, CMML cytogenetic risk classification, and red cell transfusion dependency [23]. With increased understanding of the molecular nature of CMML, the Groupe Francophone des Myelodysplasies (GFM) group proposed a prognostic score based on *ASXL1* mutations, age, hemoglobin, WBC, and platelet counts that defined three prognostic groups with median OS of 56, 27.4 and 9.2 months [24] This differed from a model proposed by Mayo clinic, as only nonsense

and frameshift mutations of ASXL1 were included, the Mayo model included all ASXL1 mutations, which was not prognostic [25]. The Mayo Molecular Model confirmed the prognostic implication of ASXL1 frameshift and nonsense mutations [15]. The CPSS was also updated to include molecular data and found on multivariate analysis the following mutations were independently prognostic: RUNX1 (HR = 2.32, P = .016), NRAS (HR = 2.19, P = .009), SETBP1 (HR = 2.00, P = .04), and ASXL1 (HR = 1.77, P = .022) [13].

1.3. Management of CMML

Due to the heterogeneity of disease with CMML, management can be challenging. Some patients will have an indolent course with median survival in excess of 10 years, whilst others progress rapidly to AML. Allogeneic Hematopoietic Cell Transplantation (Allo-HCT) remains the only treatment modality associated with long term remissions and long-term OS benefit (10-year OS rate of 40%). Factors associated with favorable outcomes appear to be low CMML risk group, adequate pre-transplant hematocrit, favorable cytogenetic risk category, low co-morbidity index, and younger age [26]. Splenomegaly at the time of Allo-HCT was reported to be associated with worse OS and EFS post-transplant [27]. Splenomegaly is a major source of morbidity in approximately 30%-50% of patients with CMML and is associated with abdominal discomfort, left subcostal pain and early satiety, as well as serious risk of splenic rupture and splenectomy sequelae [28, 29]. The effectiveness of splenectomy in alleviating many of the symptoms of CMML was demonstrated in a study of patients with CMML where splenectomy was medically necessary. In one study, 85% of patients who underwent a splenectomy achieved durable resolution of symptoms. However, splenectomy was also associated with perioperative morbidity and mortality rates of 43% and 13%, respectively [29]. While the asymptomatic low risk patients can be observed until disease progression [30], CMML patients with JAK2-V617F mutations may respond to ruxolitinib [31], those with t (5;12) translocation associated with ETV6-PDGFR-$_{B}$ fusion gene might respond to imatinib mesylate [30, 32, 33], and patients with CMML associated with systemic mastocytosis (SM-AHN) with KIT D816V mutation can responds to midostaurin [34, 35]. At present, there are no satisfactory non-transplant treatment options, and the only US FDA-approved therapies are supportive therapy and two Hypomethylating Agents (HMAs), Azacitidine (AZA) and Decitabine (DEC) [28, 30, 36-38]. While these agents may transiently improve cytopenias in patient with CMML with dysplastic features, treatment outcomes are less favorable in patients with CMML with proliferative features [28, 31, 39] Recently in a retrospective analysis, Venugopal S, et al reported a series of 286 CMML patients treated with HMAs between 2004 and 2019, with an ORR of 61% in entire cohort, median overall survival of 2 years and interestingly RAS/MAPK pathway mutations and TET2/ASXL1 co-mutations did not affect survival outcomes in either D-CMML or P-CMML [40]. Azacitidine (AZA) was approved in 2004 for the treatment of patients with several MDS subtypes, including CMML. Multiple studies using AZA monotherapy for CMML reported overall response rate (ORR) and complete remission (CR) rate of 39-60% and 11-40%, respectively [37, 41-43]. The SWOG S1117 phase II/III randomized study (n= 277) of AZA alone or in combination with Lenalidomide (LEN) or with Vorinostat (VOR) in high risk MDS and CMML with median follow up of 23 months showed ORR of 38%, 49%, and 27%, respectively. In this

study, patients with higher risk MDS had similar ORR in all arms, however the CMML subgroup had higher ORR with AZA/LEN compare to AZA alone (68% Vs. 28%, p= 0.02) [44]. Decitabine (DEC) was approved in 2006 for the treatment of patients with all MDS subtypes, including CMML. In two retrospective analysis of DEC in the treatment of CMML the ORR ranged 26-68% with 2-year survival range of 25-48% [45, 46]. Braun T, et al. in a phase 2 trial of DEC 20 mg/m2 on days 1-5 of a 28 days cycles showed ORR of 38% with 2-year survival rate of 48% [47]. Additionally Santini et al. reported ORR of 47.6% with a significant longer survival in responders (p=0.02) in a phase 2 multicenter trial in higher risk CMML receiving DEC for 5 days of a 28 days cycle [38]. Cytoreductive agents such as Hydroxyurea (HU) or cytarabine can reduce leukocytosis and, very rarely, splenomegaly in CMML with proliferative features, but usually worsen cytopenias and have modest impact on disease-associated symptoms [28] Subsequent to the HMA approvals in MDS, additional clinical studies of these agents in CMML have demonstrated ORR centered at approximately 30-40% (range-25% to 75%) upon initial exposure to HMAs, but responses were generally not sustained with Complete Response (CR) rates of approximately 15%, and median OS of 12 to 37 months [28, 48-51]. Clinical studies with a variety of cytotoxic drugs and targeted therapies have generally been disappointing and therapy was associated with significant toxicities [48].Given these results, there is a need for additional therapies for patients with CMML, and especially those who have been previously treated with or are not expected to derive benefit from treatment with an HMA. It remains challenging to determine who should receive an Allogeneic Hematopoietic Cell Transplant (allo-HCT) for CMML given the median age at diagnosis is 70 years, and the clinical heterogeneity of disease. Clinical practice tends to use MDS criteria when determining need for transplant. Ongoing questions without randomized control trials to address including the timing of transplant (which patients may benefit in CR1), and whether pre-transplant therapy with HMA or other therapies should be employed. A retrospective analysis of 406 patients at the Mayo clinic with CMML (age ≤ 75) were included, with the age cut off being the institutional limit for allogeneic transplant. 70 patients (17%) underwent allo-HCT (66% in chronic phase and 34% after blast transformation/AML), and in the propsensity score matched analysis the median OS was high in the allo-HCT group compared to non-alloHCT [40 months, (95% CI 26–NR) vs. 23 months, (95% CI 10–37, p = 0.004) [52]. In this analysis, allo-HCT achieved a 5 year OS of 51% in chronic phase CMML and 18% in blast transformation CMML, suggesting earlier transplant may benefit these patients especially in higher risk subgroups by prognostic scoring systems. Another recent retrospective German study looked at 261 patients with CMML ≤ 70 years, and described outcomes in patients who underwent allo-HCT and those who did not, and found a significant OS advantage in those who had allo-HCT for higher risk (intermediate-2/high by CPSS) with 37% reduced HR for death [53]. Patients with lower risk (low/intermediate-1 CPSS) had similar outcomes with or without transplantation. This study excluded patients who had blast transformation and noted the patients undergoing transplant were younger with a median age of 58 compared to 65 in the nontransplant group. They also reported no survival difference in patients who received treatment with HMA prior to transplant compared to those who did not, although they did not collect full regimen data.

1.4. Assessing Response to CMML Therapy

Historically, based on CMML's original classification as an MDS, clinical studies enrolling CMML patients had responses measured via the International Working Group (IWG) response criteria for MDS [54]. However, it was subsequently observed that approximately 50% of patients with CMML predominantly present with myeloproliferative, rather than myelodysplastic features [55]. The MDS/MPN International Working Group recommended new response criteria to measure treatment response in MDS/MPN, including CMML, to capture measures of clinical benefit relating to CMML with proliferative features, now referred to as overlap-MDS/MPN criteria [56]. This includes assessing both peripheral blood and bone marrow blast reduction, improvement in cytopenias, WBC, monocyte and immature myeloid cell normalization, decrease in splenomegaly or extramedullary hematopoiesis, correction of myelofibrosis, and has a provisional entity of clinical benefit based on MPN-SAF score [42]. Currently, the molecular and clinical heterogeneity along with the absence of uniform response criteria to assess meaningful therapeutic benefit make developing and comparing new therapies a challenge. Novel agents that target biological features important in MDS/MPN are in development; testing the effectiveness of these with a harmonized assessment approach designed specifically for MDS/MPN will be important to accurately assess the impact of these treatments. A retrospective validation was performed to assess the revised criteria by the international consortium for MDS/MPN outcome analysis of 79 patients with CMML. In this analysis, response status between the IWG 2006 criteria and newer MDS/MPN criteria was concordant in 86% of cases, and both sets of response criteria led to similar predictive power for OS. Notably, the more stringent definition of progression by the MDS/MPN criteria was described by the authors as 'relevant', as 6 patients who had PD per the IWG 2006 criteria at first assessment finally achieved response, whereas no patients with progression per overlap-MDS/MPN achieved response [57]. The 2018 European Hematology Association/European Leukemia Net (EHA/ELN) expert panel for CMML recommends PB and bone marrow aspirate (cytology) assessment as mandatory; bone marrow biopsy is considered useful for the diagnosis as it allows the assessment of cellularity, description of stroma, of fibrosis, and detects the rare association of mast cells (in patients with concomitant Systemic Mastocytosis [SM] and CMML). Suggested immunohistochemistry and flow cytometry immunophenotyping include CD34 and the monocytic markers CD68, CD163, CD14, and CD16. $CD14^{\pm}/CD16^{-}$ monocytes are considered `classical' and are proposed as biomarkers to monitor response to therapy. Cytogenetic analysis and the assessment of 4 genes -*ASXL1*, *NRAS*, *RUNX1*, and *SETBP1* were considered mandatory. The panel also recommends that while the MDS/MPN 2015 criteria require additional validation in CMML, it is preferable to use the IWG 2006 criteria for monitoring response to treatment. For patients with splenomegaly, the panel recommended an imaging technique (ultrasound, Computed Tomography [CT] or Magnetic Resonance Imaging [MRI]) rather than physical examination alone. Symptom burden has not been studied specifically in CMML and the use of Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) as an initial tool for symptom assessment is reasonable.

1.5. Future directions/Current treatment

Bcl-2 overexpression has previously been reported as an escape mechanism in patients resistant to HMA in myelodysplastic syndromes, and studies in CMML treated with Venetoclax (VEN) based therapy are emerging [58]. A retrospective study of 53 patients who received VEN for CMML (any line) or frontline for patients with AML with myelodysplastic related changes from preceding CMML was reported from MD Anderson with promising results [59]. Patients with CMML had an ORR of 67% - most of which were partial responses, and patients with AML-MRC had ORR of 81% with 62% composite CR; of the patients with CR/CRi 47% had MRD negative CR. The authors highlight CMML may have features prone to VEN resistance, as approximately 30% of patients with CMML will have RAS/MAPK mutations, which have been associated with upregulations of Myeloid Leukemia Cell Diffierentiation Protein 1 (MCL1), a known resistance pathway for Bcl-2 inhibition [60]. A similar retrospective series of VEN based therapy was reported on 32 patients with CMML and CMML with blast transformation with ORR reported 59% (CR 0%, mCR 53%, PR 6%) in the CMML and 67% (CR/CRi 53%, MLFS 7%, PR 7%) in the blast transformation group. The majority of CMML patients were treated with VEN in combination with HMA, however the blast transformation group combinations included HMA (47%), intensive chemotherapy (20%) or other agents (33%). This study again highlights the ability of VEN to clear blasts, however most patients with CMML achieved a partial response While RAS mutations were associated with lower CR rates [61]. Recently, Seven et al. has reported monocyte resistance to apoptosis in CMML as an ‘addiction’ to MCL-1 (by BH3 profiling), and by upregulation of CYTL1 and activation of the MAPK/ERK pathway [62]. Targeting both of these pathways with MCL-1 and MAPK (MEK) inhibitors restored apoptosis of monocytes in xenografted mice and prevented leukemic infiltration in tissues, without significant impact on normal monocytes. They propose further testing in the clinical setting. Islands of CD123 cells have been commonly described in the bone marrow of patients with CMML [63]. Using a multiparameter flow cytometry assay, an excess of $CD123^{+}$ mononucleated cells in the bone marrow of 32/159 (20%) patients were detected in a recent study and characterized as plasmacytoid dendritic cells (pDCs) [64]. Furthermore, an excess of pDCs correlates with regulatory T cell accumulation and an increased risk of acute leukemia transformation. These results demonstrate the FLT3-independent accumulation of clonal pDCs in the bone marrow of CMML patients with mutations affecting the RAS pathway, which is associated with a higher risk of Progressive Disease (PD) [64]. Updated results of an ongoing phase ½ trial of Tagraxofusp (SL- 401) in CMML patients showed significant clinical activity particularly in those with baseline splenomegaly (42% response) [65]. In patients that may have difficulty traveling or with infusions, oral decitabine/cedazuridine may be an option as well. Efficacy of oral Decitabine/Cedazuridine (ASTX727) was evaluated in the CMML subgroup from the Ascetain phase 3 showed ORR of 75% with Leukemia free survival rate of 28.2 months, indicating this drug as a reasonable treatment option in this group of patients [66]. As the molecular landscape continues to unfold in CMML, the efficacy of therapeutics in different subsets of disease will continue to unfold and help distinguish which patients benefit from allogeneic transplantation. Due to the relatively small number of cases of CMML, multicenter registry data will be important to continue answer further questions regarding this disease.

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