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REVIEW

Chronic myelomoncytic leukemia: Are we finally solving the identity crisis?

Aziz Nazha [a], Thomas Prebet [b], Steven Gore [b], Amer M. Zeidan [b,*]

[a] Leukemia Program, Department of Hematology and Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA
[b] Section of Hematology, Department of Internal Medicine, Yale University, and Yale Comprehensive Cancer Center, New Haven, CT, USA

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ABSTRACT

Chronic myelomonocytic leukemia (CMML) is a unique disease entity with overlap components of both myelodysplastic syndrome and myeloproliferative neoplasms. CMML is a clonal hematopoietic stem cell neoplasm characterized by monocytosis, cytopenias, and extramedullary manifestations such as splenomegaly. The disease is rare and has undergone revisions in its classification. We review the recent classification strategies as well as diagnostic criteria, focusing on the new insights into the genetic alterations and unique pathophysiology of the disease. We also discuss the latest molecular characterization of the disease, including how molecular factors affect current prognostic models. Finally, we focus on available treatment strategies, with a special emphasis on experimental and forthcoming therapies.

1. Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell neoplasm generally recognized as a chronic leukemia with persistent monocytosis and features reminiscent of myeloproliferative neoplasms (MPN) and myelodysplastic syndromes (MDS) [1]. Although CMML has been recognized as a distinct disease for more than 40 years, it was not until 1978 when it was defined as a subcategory by the French–American–British (FAB) classifications [2,3] [Table 1]. The FAB group subsequently classified CMML into two subgroups based on white blood cell count: MDS-CMML with WBC less than 13×10^9/L and MPN-CMML with WBC equal of greater than 13×10^9/L. Since that time, significant debate arose whether CMML should be classified as a distinct entity with overlapping features between MDS and MPNs. The World Health Organization (WHO) subsequently classified CMML as distinct entity within a provisional category in 2002 and later reclassified it under myelodysplastic/myeloprolifrative overlap neoplasms (MDS/MPN) [4,5]. This group of disorders also include: atypical chronic myeloid leukemia (aCML), juvenile myelomonocytic leukemia (JMML), and MDS/MPNs unclassifiable [5].

Although the pathophysiologic underpinnings of CMML remain poorly understood, recent advances in genomic technologies have identified several chromosomal and molecular abnormalities that define the genomic fingerprint of CMML although none of these abnormalities is pathognomonic for CMML [6–8]. Since CMML was formerly categorized as a subtype of MDS, most of the current treatment recommendations and clinical trial data for CMML have been mainly based on therapy directed for patients with MDS. However, more recent data are becoming increasingly available to aid in evidence-based management of CMML [8,9]. In this paper, we discuss the current knowledge of the epidemiology of the disease, the clinical features, classification and diagnosis of CMML, and review current insights into its pathophysiology. We also discuss established and state-of-the-art treatment options for patients with CMML, and overview some of the investigational agents in advanced clinical development for CMML.

2. Epidemiology and presentation

The actual incidence of CMML is unknown but epidemiological studies suggest that the age-adjusted incidence of CMML in the United states is 0.3 per 100,000 using SEER (Surveillance, Epidemiology, and End Results) database and 0.39 per 100,000 in a Spanish registry [10,11]. The actual incidence of CMML may be higher than derived from cancer registries because of misdiagnosis or misclassification as MDS. CMML is rarely diagnosed in younger adults, with the median age at diagnosis of 65 to 70 years, approximating the reported median diagnosis age of patients with MDS. It has been reported that patients with MPN-CMML were older with more male predominance than patients with MDS-CMML, but these differences were not statistically significant [12,13].

Therapy-related CMML is rare, accounting for approximately 11% of all cases, and appears to carry an overall worse outcome [14]. Secondary CMML defined as CMML arising from antecedent cases of MDS has been also described in approximately 6% of all CMML cases [15]. Although environmental exposures have not been directly linked to CMML, some

* Corresponding author at: Section of Hematology, Department of Internal Medicine, Yale University, 333 Cedar Street, P.O. Box 208028, New Haven, CT 06520-8028, USA. Tel.: +1 203 737 7103, fax: +1 203 785 7232.
E-mail address: amer.zeidan@yale.edu (A.M. Zeidan).

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Table 1
French–American–British (FAB) and World Health Organization (WHO) 2008 Classification of CMML. Abbreviations: FAB, French–American–British; WHO, World Health Organization, CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; PB, peripheral blood; MD-CMML, myelodysplastic CMML; MP-CMML, myeloproliferative CMML.

FAB classification	WHO classification
MDS	MDS/MPD overlap syndrome
1. PB Monocytes $>1 \times 10^9$/L (defining feature) 2. Myeloblasts <20% in bone marrow 3. PB blasts <5%	1. PB Monocytes $>1 \times 10^9$/L 2. Myeloblasts <20% in bone marrow 3. No Philadelphia chromosome or *BCR-ABL1* fusion gene 4. No rearrangement of *PDGFRA* or *PDGFRB* (excluded especially in cases with eosinophilia) 5. Dysplasia in at least one myeloid lineage. If myelodysplasia is absent or minimal, diagnosis can still be made if the other requirements are present and: ✓ An acquired clonal cytogenetic or molecular genetic abnormality is present *or* ✓ The monocytosis has persisted for at least 3 months *and* all other causes of monocytosis have been excluded (e.g. infection, inflammation, malignancy)
Subclassification	**Subclassification**
MD-CMML: WBC $\leq 13 \times 10^9$/L MP-CMML: WBC $>13 \times 10^9$/L	CMML-1: PB blasts <5%, BM blasts <10% CMML-2: PB blasts 5–19%, BM blasts 10–19%, or Auer rods present CMML-1 or CMML-2 with eosinophilia: above criteria with PB eosinophils $>1.5 \times 10^9$/L

investigators speculate that given the similar age of at diagnosis and the overlapping clinical and pathological features of CMML and MDS, known environmental exposures such as ionizing radiation, cytotoxic chemotherapy, agricultural chemicals, and tobacco smoking that are recognized risk factor for MDS may also be valid for CMML.

3. Biology and pathophysiology

The pathophysiology of CMML is still not fully understood, mainly because CMML has been infrequently studied as a separate entity rather than as a subtype of MDS. The high variability of clinical presentations and disease course reflect the heterogeneity of its underlying pathogenetic features. Still, multiple theories based on cellular, cytogenetic, and molecular abnormalities supported by observation from animal models have been developed over the past two decades. Although some mouse models have myelomonocytic features that resemble CMML, this may represent a function of murine hematopoiesis rather than a good model for CMML.

Decreased apoptosis as an alternative pathway to tumorigenesis has been described in myeloid leukemogenesis including CMML. Similarly, increased expression of Bcl-2, Bcl-xL (antiapoptotic), Bax, Bad, Bak, and Bcl-xS (proapoptotic) as well as cyclin D1 have been reported in patients with CMML [16,17]. Further, activating mutations in RAS pathway predominantly NRAS can function as ancestral oncogene that is sufficient of inducing CMML or AML-like disease in mice highlighting the importance of NRAS mutation as initiating oncogene in CMML and myeloid malignancies [18].

Angiogenesis has also been shown to play an important role in CMML leukemogenesis. Pruneir et al. showed significant increases in microvascular density (MVD) in patients with CMML and MDS [19]. Furthermore, the plasma levels of vascular endothelial growth factor (VEGF), hepatocyte growth factor, and tumor necrosis factor α (TNF-α) were significantly elevated in patients with CMML compared to control [20].

At the molecular level, CMML is substantially different from the other myeloproliferative diseases. Single cell derived colonies assay in patients with CMML showed linear acquisition of mutations with early clonal dominance arising from the multipotent and common myeloid progenitors. More importantly, serial analysis of untreated and treated samples demonstrated the lack of efficacy of current therapeutic approaches on the clonal architecture of the disease [21].

Mutations in the JAK2 pathway, leading to activation of the JAK/STAT pathway, as prominent feature of MPNs [22,23] are rare in CMML. Nevertheless, recent data suggested hypersensitivity to granulocyte-macrophage–colony-stimulating factor and phospho-STAT-5 [24]. Hypersensitivity to phospho-STAT5 is associated with higher risk disease, peripheral leukocytosis, and signaling-associated mutations [24]. More importantly, treating primary CMML cells with JAK2 inhibitors showed decreased viability of immature myeloid and monocytic progenitors [24]. These observations have led to the development of clinical trial with ruxolitinib (JAK2 inhibitor) in patients with CMML that is currently underway.

In contrast, among hematologic malignancies, CMML is associated with the highest incidence of RAS pathway mutations [25]. Animal models have supported the theory that the RAS activation pathway may be a significant contributor to myeloproliferation in CMML [26]. Irradiated mice that undergo NRAS mutated bone marrow cell transplantation develop myeloproliferative/like disease resembling CMML [26].

TET2 mutations were among the most commonly described mutations in CMML occurring in 20–44% of patients [27–29]. Clonal expansion of TET2-mutated clone obtained from CMML samples showed correlation between the proportion of cells that carry TET2 mutations and peripheral monocyte counts. Further, in analysis of single cell derived colonies from patients with CMML, functional knockdown of TET2 in CD34+/CD38- cells caused a granulomonocytic expansion that was not observed in CD34+/CD38+ suggesting that early dominance of TET2-mutated clone may contribute to granulomonocytic skewing that yield to CMML development [21].

SRSF2 mutations were also described in high frequency in patients with CMML. In a large study of 275 patients with CMML, 47% of patients had SRSF2 mutations [7]. SRSF2 mutations correlated with advanced age, less pronounced anemia, normal karyotype and were mutually exclusive with EZH2 [7]. In another study of 266 patients with CMML, SRSF2 mutations were identified in 40% of patients with CMML and were mutually exclusive with other spliceosome mutations [30,31].

Mutations in ASXL1 were also common in CMML accounting for 49–58% of patients with CMML [32–34] and the presence of these mutations is associated with poor outcome [32–34].

4. Diagnosis

The 2008 WHO diagnostic criteria for CMML require persistent unexplained peripheral monocytosis $>1 \times 10^9$/L. It is very important to rule out other causes of monocytosis before initiating the workup for myeloid neoplasm such as infections with tuberculosis, chronic fungal infections, and protozoal infections as well as connective tissue disease such as systemic lupus erythematosus and sarcoidosis. After ruling out all causes of reactive monocytosis, a bone marrow biopsy and aspiration is an essential element of the diagnostic workup and should also include conventional cytogenetic analysis and florescence in situ hybridization if no dividing cells are observed with G-banding. There is no single pathognomonic diagnostic feature of CMML but rather a collection of histopathologic and immunophenotypic features. Thus it is essential to rule out other myeloid malignancies such as chronic myeloid leukemia (CML) by screening for BCR-ABL fusion gene and chronic eosinophilic leukemia (CEL) by ruling out the presence of PDGFRA or PDGFRB rearrangement.

Morphological assessment of bone marrow aspirate by an experienced hematopathologist is of paramount importance to establish the diagnosis of CMML. Identifying dysplastic changes in at least 10% or