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Chronic myelomonocytic leukemia: Forefront of the field in 2015

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Abstract

Chronic myelomonocytic leukemia (CMML) includes components of both myelodysplastic syndrome and myeloproliferative neoplasms and is associated with a characteristic peripheral monocytosis. CMML is caused by the proliferation of an abnormal hematopoietic stem cell clone and may be influenced by microenvironmental changes. The disease is rare and has undergone revisions in its classification. We review

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the recent classification strategies as well as diagnostic criteria, focusing on CMML's genetic alterations and unique pathophysiology. We also discuss the latest molecular characterization of the disease, including how molecular factors affect current prognostic models. Finally, we focus on available treatment strategies, with a special emphasis on experimental and forthcoming therapies.

Keywords: Chronic myelomonocytic leukemia; Myelodysplastic syndrome; Myeloproliferative neoplasms

1. Introduction

Chronic myelomonocytic leukemia (CMML) is generally recognized as a chronic leukemia with persistent monocytosis and components of both myeloproliferative neoplasms and myelodysplastic syndrome [1]. It has been recognized as a distinct disease for more than 40 years, although until 2002 it was grouped with myelodysplastic syndrome (MDS). In 1971, Saarni and Linman recognized qualitative abnormalities in more than one lineage in patients with monocytoid leukemic transformation; 36% of their patient series had peripheral monocytosis, and 31% demonstrated a preleukemic phase, sometimes for as long as 9 years [2,3]. The term *myelomonocytic leukemia* denotes both the myeloid and the monocytoid features of the disease. In 1972, Zittoun et al. described 27 cases of subacute myelomonocytic leukemia [4,5]. The first significant-size cohort of patients to be recognized as having CMML was described in 1975 and included 18 elderly patients with unexplained monocytosis, cytopenias, and splenomegaly [6,7]. Five of the patients survived longer than 5 years. This finding indicated that intensive chemotherapy may not be needed in this patient population and led to recognition of CMML as a distinct entity by the French–American–British (FAB) Group in 1976 [8]. Since then, several groups have categorized the clinical manifestations and outcome of CMML as a subset of MDS. However, some patients with CMML may express features of myeloproliferative neoplasms (MPN; also known as myeloproliferative disorders or MPD) at the time of diagnosis or at another stage in the course of the disease. Consequently, CMML has remained under-researched and is often excluded from MDS and MPN clinical trials.

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

2. Classification and diagnosis

2.1. FAB and WHO classifications

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

Nosslinger et al. conducted a retrospective analysis of 91 patients with CMML who had been treated primarily with supportive care [11]. At the time of diagnosis, patients with MP-CMML (*n*, 31; 34%) had higher lactate dehydrogenase (LDH) levels, absolute neutrophil counts, and bone marrow cellularity values than did patients with MD-CMML (*n*, 60; 66%). The median overall survival (OS) duration for the MP-CMML group (16 months) was significantly shorter than that for the MD-CMML group (31 months) (*p*-value, 0.03), with a higher risk of leukemia transformation in the MP-CMML group, indicating differences in outcomes between the two groups. Onida et al. retrospectively analyzed 213 patients with CMML treated with various approaches, including chemotherapy, and classified each patient's CMML as MD-CMML (*n*, 74; 35%) or MP-CMML (*n*, 139; 65%) on the basis of the patients' WBC counts [12]. Although the OS rates were similar in the first few months of treatment, a significant difference appeared after 16 months, with a higher OS rate for MD-CMML patients. The difference in rate of leukemic transformation, however, was not statistically significant [12]. Voglova et al. analyzed 69 patients with CMML, 31 (45%) classified as MD-CMML and 38 (55%) as MP-CMML [13]. Cytogenetic abnormalities were more frequent among patients with MP-CMML. The median OS was significantly longer in the MD-CMML group than in the MP-CMML group (30 vs. 16 months, respectively; *p*-value <0.01), and there was no significant difference in leukemic transformation. However, in 24 patients with MD-CMML, the WBC count increased to more than $13 \times 10^9\,L^{-1}$ over the course of the disease. The authors concluded that using the WBC count obtained at diagnosis as the single criterion