

# Leukaemia Section

## Mini Review

# Chronic Myelomonocytic Leukemia (CMML)

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## Identity

### Note

The nosology of CMML is controversial. The FAB classification categorized this disorder as a myelodysplastic disorder. Others view this disease as predominantly a myeloproliferative disorder, or recognize both myeloproliferative and myelodysplastic forms of CMML. The recent World Health Organization (WHO) classification places CMML into a separate category along with juvenile myelomonocytic leukemia (JMML, JCML) of disorders with both myelodysplastic and myeloproliferative features.

## Clinics and pathology

### Disease

The defining features of CMML are an absolute monocytosis of  $>1 \times 10^9/l$ , increased numbers of monocytes in bone marrow, and a variable degree of dysplasia in all three lineages. Myeloblasts and promonocytes comprise less than 5% of nucleated cells in peripheral blood and less than 20% of cells in bone marrow. Roughly half of patients present with an elevated white cell count that is commonly associated with hepatomegaly and splenomegaly, the so-called myeloproliferative form of the disease. Patients lacking these features are generally considered to have the myelodysplastic form of the disease.

### Phenotype/cell stem origin

Presumably a multipotential stem cell.

### Epidemiology

CMML is usually a disease of older adults although the disease also occurs in children, where distinction from juvenile chronic myelogenous leukemia (JCML,

also known as juvenile myelomonocytic leukemia) is difficult, and at times impossible. In one series the median age for the myelodysplastic type was 70 and for the myeloproliferative form 72 years. The disease shows a distinct male predominance of 1.6-2.1:1.

### Clinics

CMML patients may present with hepatomegaly or splenomegaly, serous effusions or other sites of extramedullary involvement such as skin or, less commonly, gums.

### Cytology

Blood: The peripheral blood count may be increased or decreased. By definition monocytes and promonocytes exceed  $1 \times 10^9/l$ . Dysplastic monocytes or neutrophils are usually evident. Normocytic or macrocytic anemia is common as is thrombocytopenia, which is usually mild. Serum lysozyme is usually elevated and immunoglobulin elevations occur in about a third of patients, with monoclonal gammopathy in about 5-10% of patients.

Bone marrow: The bone marrow is almost always hypercellular, often with trilineage dysplasia. Myeloblasts and monoblasts are less than 20% of the total cellularity. About 30% of cases show significant reticulin fibrosis. Cases associated with the t(5;12) (see below) are commonly associated with eosinophilia.

### Treatment

Although CMML often initially respond to conventional chemotherapy, complete responses are rare. Allogeneic bone marrow transplantation is potentially curative for those patients who are eligible.

### Prognosis

The median survival for patients with CMML is about 24 months. There does not appear to be a difference in survival between patients with the myeloproliferative

versus the myelodysplastic forms of the disease nor are the number of blasts of prognostic value. Of adult patients who underwent allogeneic bone marrow transplantation the disease-free survival was 39% at 3 years.

## Cytogenetics

### *Cytogenetics morphological*

By definition CMML cases do not show the Philadelphia chromosome. Overall 20-30% of cases show cytogenetic abnormalities. These include numerical and structural abnormalities such as +8, del(20q), -7, del(11q), all of which may be seen in other myelodysplastic and myeloproliferative disorders. Rarely translocations have been identified in CMML. Cases associated with eosinophilia commonly show t(5;12)(q33;p13) which fuses TEL to the platelet-derived growth factor receptor (PDGFR) (about 2-5% of all CMML cases). Fusions of the Huntington interacting protein 1 (HIP1) gene to PDGFR have also been described in CMML associated with t(5;7)(q33;q11.2). Occasional cases of therapy-associated CMML are associated with the t(11;16)(q23;p13) which fuses MLL to CBP. Rare reports of CMML associated with t(1;13)(p36;q21), t(7;11)(p15;p15) and t(8;9)(p11;q34) have been reported.

## Genes involved and proteins

### Note

**Mechanisms of Oncogenesis:** In most cases of CMML the critical genetic lesions have not been identified. In the case of the TEL-PDGFRb fusion the TEL HLH region mediates oligomerization of the PDGFR that appears to be required for its mitogenic properties. Roughly half of CMML cases show mutations of K-RAS and N-RAS, usually glycine to aspartic acid substitutions at the 12th or 13th codons.

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