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Leukaemia Section
Short Communication

Chronic Myelomonocytic Leukemia (CMML)

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Abstract: Short communication on Chronic Myelomonocytic Leukemia, with data on clinics, and the genes involved.

Identity

Chronic Myelomonocytic Leukemia (CMML)

Note
Chronic myelomonocytic leukemia (CMML) is the most frequent entity among myeloproliferative / myelodysplastic syndromes, as defined by the World Health Organization (WHO) classification of myeloid malignancies in 2008. The percentage of peripheral and marrow blast cells is the major prognostic factor identified at that time. Based on the percentage of blast cells in the bone marrow and peripheral blood, CMML is further stratified into CMML-1 (< 5% in blood, < 10% in the bone marrow) and CMML-2 (5 - 19% in the blood; 10 to 19% in the bone marrow, or less if Auer inclusions are present).

Clinics and pathology

Disease

Note
The WHO criteria include 1) stable increase in peripheral blood monocyte count (> 1 x 10^9/L); 2) lack of Philadelphia chromosome and BCR-ABL fusion gene; 3) lack of gene rearrangement involving the Platelet-Derived Growth Factor Receptor Beta gene (PDGFRB); 4) blast cell percentage in the blood and the bone marrow lower than 20% and 5) cellular dysplasia of at least one myeloid cell line. This last criterion is not mandatory, as monocyte dysplasia can be difficult to assess in the bone marrow, and dysplasia of other lineages is inconstant. Thus, CMML may not always have a cytologically identifiable dysplastic component. When dysplasia is missing, diagnosis can be made if a clonal cytogenetic or molecular abnormality is identified in hematopoietic cells, or if peripheral blood monocyte count remains elevated at least 3 months without any other explanation.

Phenotype/cell stem origin

The cell of origin is a multipotential stem cell.

Epidemiology

CMML is a relatively rare disease whose incidence is around 1 case/100000 inhabitants per year. CMML is a disease of older adults, with a strong male predominance. The median age at diagnosis is around 70 years, the disease is exceptionally diagnosed before 50 years of age.

Clinics

The onset of the disease is usually insidious and, diagnosis is fortuitous in many cases. Symptoms, when present, are the consequences of cytopenias (notably anemia, which is invalidating in a third of patients), and/or of extramedullary hematopoiesis, notably splenomegaly but also hepatomegaly, skin infiltration, gum infiltration, and serous (notably pleural) effusions. Extramedullary hematopoiesis is mostly restricted to patients with WBC > 13 G/L. Finally, auto-immune manifestations (seronegative arthritis, vasculitis) can be associated to CMML.

Cytology

Peripheral blood count indicates monocytosis (up to 80 x 10^9/L). Cells identified by cytologists as monocytes are heterogeneous, commonly including mature monocytes, dysplastic monocytes, and a variable

fraction of dysplastic granulocytes (these cells do not express CD14 but express granulocytic markers CD15 and CD24, belong to the leukemic clone, and demonstrate immunosuppressive properties like myeloid-derived suppressive cells). An increase in neutrophils or eosinophils can be associated, as well as myelemia. Anemia is usually moderate, normocytic or macrocytic. Thrombocytopenia is inconstant and can be severe. Of note, an immune mechanism can contribute to these cytopenias. Hyperuricemia, increased B12 plasma level, increase serum and urine lysozyme, and polyclonal hypergammaglobulinemia can be observed.

Bone marrow: Bone marrow smears show a hypercellular tissue in which blast cell percentage (myeloblasts and monoblasts) remains lower than 20%. Monocyte proliferation is always present and often moderate (10 to 15% of mononuclear cells) and dysplastic changes can be observed in one or several lineages. A variable degree of myelofibrosis can be detected in up to 30% of patients.

Treatment

Allogeneic stem cell transplantation remains the only potentially curative option but is rarely feasible, due to the age of patients. In those ineligible for transplantation, the mainstay of CMML treatment is hydroxyurea, which is usually initiated when the disease becomes proliferative. The overall response rate reaches 60% but complete response is exceptional.

The hypomethylating agent azacitidine (AZA) has been approved in Europe for CMML with WBC < 13 G/L and bone marrow blasts between 10 and 29%.

The other hypomethylating agent, decitabine, is approved in US, not in Europe. An overall response rate of 40% is observed with these drugs. Prospective randomized comparisons of hypomethylating agents versus hydrxyurea have still to be performed.

Prognosis

The median survival for patients with CMML is 24-36 months. According to the WHO, the main prognostic factor is the percentage of blast cells in the blood and the bone marrow. Several prognostic scores have been proposed that rely on peripheral blood counts, serum lactate deshydrogenase values, and percentage of bone marrow blast cells and cytogenetic abnormalities. More recent data suggest that cytogenetic and molecular information could be prognostically useful. Cytogenetics is part of a recent Spanish score whereas a recent French prognostic score includes the presence of mutations in ASXL1 gene, which is an independent poor prognostic factor in CMML. An international staging system may be established in the coming years.

Cytogenetics

Cytogenetics morphological

Conventional metaphase karyotyping of bone marrow mononucleated cells is normal in two thirds of patients. By definition CMML cases do not show the Philadelphia chromosome.

Cases associated with eosinophilia and rearrangements that fuse the platelet-derived growth factor receptor (PDGFRB) to another gene such as TEL in t(5;12)(q33;p13) are excluded from the CMML group by the WHO classification as this separate entity is sensitive to tyrosine kinase inhibitors such as Imatinib mesylate.

The recurrent aberrations observed in CMML include loss of the Y chromosome, monosomy 7, trisomy 8, and interstitial deletions of chromosomes 20q, 11q, and 12p, all of which may be seen in other myelodysplastic and myeloproliferative disorders.

The proportion of patients showing large areas of uniparental disomy (UPD) in their blood cells, which is about 50% and could result from mitotic recombinations, is higher than in other myeloid malignancies.

Genes involved and proteins

Note

Whole exome sequencing identifies a mean number of 16 mutations in peripheral blood monocytes of patients with a CMML, none of which is specific of this entity. The recurrently mutated genes encode signaling molecules (NRAS, KRAS, CBL, JAK2, FLT3, CSF3R, NOTCH, NCSTN, MAML1), epigenetic regulators (TET2, ASXL1, EZH2, UTX, IDH1, IDH2, DNMT3A, SETBP1), splicing factors (SF3B1, SRSF2, ZRSF2, U2AF1), and cohesins (STAG1, STAG2, RAD21, SMC1A, SMC3, PDS5B).

Mutations in the transcription regulators RUNX1, NPM1 and TP53 have also been reported in CMML. The most frequently mutated genes are TET2 (50-60%), SRSF2 (40-50%), and ASXL1 (30-40%).

TET2 and SRSF2 mutations are often combined. Most of the studies consistently report the poor prognosis of ASXL1 mutations.

Aberrant gene expression profiles can be identified in the absence of gene mutation.

In particular, expression of TIF1γ (transcription intermediary factor 1 gamma) is repressed by aberrant promoter hypermethylation in 35% of CMML patients, and conditional invalidation of TIF1γ leads to a CMML-like syndrome in aging mice. No direct link was identified between the repression of TIF1γ and other genes such as INK4B and the epigenetic gene mutations.

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