

Answers for the CME: CMML

Q1 - F, F, T, T, F

Q2 - T, T, F, T, T

Discussion

According to the fifth edition of the WHO Classification of Haematolymphoid Tumours: Myeloid and histiocytic / dendritic neoplasms, persistent absolute ($\geq 0.5 \times 10^9/L$) and relative ($\geq 10\%$) peripheral blood monocyto-sis is required as the first criterion for the diagnosis of CMML¹. **The previous cut off level for monocyto-sis has been lowered to $\geq 0.5 \times 10^9/L$ to incorporate previously categorised oligomonocytic CMML patients.** Other three prerequisite criteria are, having $<20\%$ blasts in the peripheral blood and bone marrow, not fulfilling the diagnostic criteria of chronic myeloid leukaemia or other myeloproliferative neoplasms and not meeting the diagnostic criteria of myeloid or lymphoid neoplasms with tyrosine kinase fusions. Presence of dysplasia involving ≥ 1 myeloid lineages, presence of acquired clonal cytogenetic or molecular abnormality and abnormal partitioning of peripheral blood monocyte subsets are included as supporting criteria. The diagnosis required presence of all 3 prerequisite criteria and one or more supporting criteria. If absolute monocyte count is ≥ 0.5 and $<1 \times 10^9/L$, both dysplasia involving ≥ 1 myeloid lineages and acquired clonal cytogenetic or molecular abnormality should be present for the diagnosis¹.

Human monocytes are divided into three subsets; CD14+/CD16- (classical), CD14-/CD16+ (non-classical) and CD14+/CD16+ (intermediate). **CMML patients have shown an increase in the fraction of classical monocytes (cut off 94%) compared to healthy subjects. However, in the presence of active autoimmune diseases monocyte repartitioning can be unreliable due to increase in intermediate type monocytes leading to a false negative result². Even though, the presence of cytogenetic abnormalities supports the diagnosis, they are not specific and only present in about 20-30% of patients². Therefore, absence of cytogenetic abnormalities does not exclude the diagnosis of CMML.**

CMML is sub grouped into CMML-1 and CMML-2 depending on the percentage of blasts (myeloblasts and monoblasts) and promonocytes in peripheral blood and bone marrow. (CMML-1: $<5\%$ in peripheral blood and $<10\%$ in bone marrow and CMML-2: 5-19% in peripheral blood and 10-19% in bone marrow). Previously introduced CMML-0 is removed from the new WHO classification considering its limited prognostic significance. CMML is also subtyped into myelodysplastic (MD-CMML) (WBC $<13 \times 10^9/L$) and myeloproliferative CMML (MP-CMML) (WBC $\geq 13 \times 10^9/L$) types depending on white blood cell count¹.

Risk assessment in CMML is important in predicting overall survival (OS) and leukaemia-free survival (LFS). It is also critical in making therapeutic decisions. CMML specific prognostic models are recommended for risk categorisation. The CMML specific MD Anderson prognostic system (MDAPS) considers Hb $<12g/dl$, presence of immature cells in the peripheral blood, absolute lymphocyte count $>2.5 \times 10^9/L$ and $\geq 10\%$ bone marrow blasts as independent predictors of inferior survival². **CMML-specific prognostic scoring system (CPSS) is another prognostic system which considered the variables: FAB and WHO CMML subtypes (CMML-MP carrying poor outcome), red blood cell transfusion dependency, and CMML specific cytogenetic risk stratification system (low: normal and isolated -Y; intermediate: other abnormalities; and high: trisomy 8, complex karyotype (≥ 3 abnormalities), chromosome 7 abnormalities) as prognostic markers¹⁻³.**

With the discovery of genetic mutations and their prognostic value, molecular prognostic tools were developed and many have been externally validated. **Among the somatic mutations, ASXL1 mutation has been associated with inferior OS and is considered in many molecular prognostic models**⁴. CPSS-mol model has incorporated RUNX1, SETBP1 and NRAS mutations which were found to be adverse prognostic factors for unfavourable survival⁵. Recommendations published by European Haematology Association and the European Leukaemia Net on diagnosis and treatment of CMML, risk stratification should be done using CMML specific models incorporating mutational analysis and recommended models are the Groupe Francophone des Myelodysplasies (GFM) CMML model, the CPSS-mol, or the Mayo Molecular Model. When mutational profiling is not available, CPSS or MDAPS models are recommended⁴.

References

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