# Challenges in the diagnosis and treatment of overlap MDS/MPN syndromes

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CMML is paradigmatic of MDS/MPN overlap syndromes. It is a rare disorder, comprising approximately 10% of all MDS cases. The median age of presentation is 65-75, and males are affected twice as commonly as females. The most common presenting features are a direct consequence of the underlying cytopenias: fatigue, susceptibility to infections and hemorrhage. Patients with more proliferative forms of the disease may present with abdominal symptoms related to splenomegaly and with constitutional symptoms associated with a hypercatabolic state: night sweats, fevers ad weight loss. More rarely patients may present with monocytic skin infiltrates or in the transformed form of the disease as AML. CMML is a pathogenetically diverse disease which lacks a specific, reliable molecular marker. There are no recurrent cytogenetic aberrations associated with this condition and most of the cytogenetic changes are those described in other forms of MDS (trisomy 8, monosomy 7 and complex karyotypes). Mutations have been described in genes involved in proliferative pathways, such as RAS, JAK2 and CBL, in tumor suppressor genes (RUNX1, TET2, ASXL1 and NPM1) and in epigenetic regulators (IHD1, IDH2 and EZH2). In addition, promoter DNA hypermethylation is found in MDS, particularly of genes within the WNT and MAPK signaling pathways. Often, multiple abnormalities are present, but these are probably secondary and the precise initiating event is not known.

In addition to the genetic aberrations detailed above, it is essential to exclude chronic infections (tuberculosis, fungal or protozoal infections, among other chronic infections) and inflammatory diseases (SLE, sarcoidosis, storage disorders) in the investigation of a patient with monocytosis as these may mimic the clinical and laboratory findings of CMML.

In general, median survival is in the range of 12 - 24 months and approximately one third of patients, depending on the series, progress to acute leukemia. Although stem cell transplantation presently represents the only potentially curative therapeutic strategy, advanced age and associated comorbidities at diagnosis often preclude this procedure.

Consequently, until recently most patients were treated with best supportive care. This includes transfusional support and erythropoiesis stimulating agents, which are usually ineffective in CMML. Patients with proliferative disease have been treated with cytotoxic agents, such as hydroxycarbamide, etoposide and cytarabine, among others, with poor response rates and significant worsening of the citopenias.

Investigations into the molecular pathophysiology of CMML have revealed marked DNA hypermethylation. This finding has been used to test the of hypomethylating agents such as 5-azacitidine (AZA) and Decitabine (DAC). Their efficacy has been firmly established in patients with higher risk MDS. The numbers of CMML patients included in large trials with these agents were few, with less than ten patients treated in the AZA trials. However, several recent reports in the literature have shown generally good safety and efficacy profiles. This experience has led to the increasing use of hypomethylating agents in all forms of CMML, including proliferative disease.

The remainder subtypes of MDS/MPN share the poor prognosis seen in CMML. Molecular markers have facilitated the diagnosis of MDS/MPN-RS-t, generally harboring JAK2 mutations, and aCML, harboring GCSF-receptor mutations. However, no directed treatment options are currently available, and most patients are treated with supportive care, highlighting the need for better knowledge of disease pathophysiology which will enable the development of better treatments.