Abstract: P696

Title: DYNAMICS OF CLONAL EVOLUTION IN CHRONIC MYELOMONOCYTIC LEUKEMIA WITH PROGRESSION TO SECONDARY ACUTE MYELOID LEUKEMIA: PAIRED-SAMPLE COMPARISON

Abstract Type: Poster Presentation

Session Title: Myelodysplastic syndromes - Biology & Translational Research

Background:

Chronic myelomonocytic leukemia **(**CMML) is an aggressive clonal hematopoietic malignancy with monocytosis and dysgranulopoiesis. CMML usually exhibits unique genetic lesions and has an aggressive prognosis with progression to secondary AML (sAML)

Aims:

This study aimed to examine the clonal architecture in the progression of CMML to sAML.

Methods:

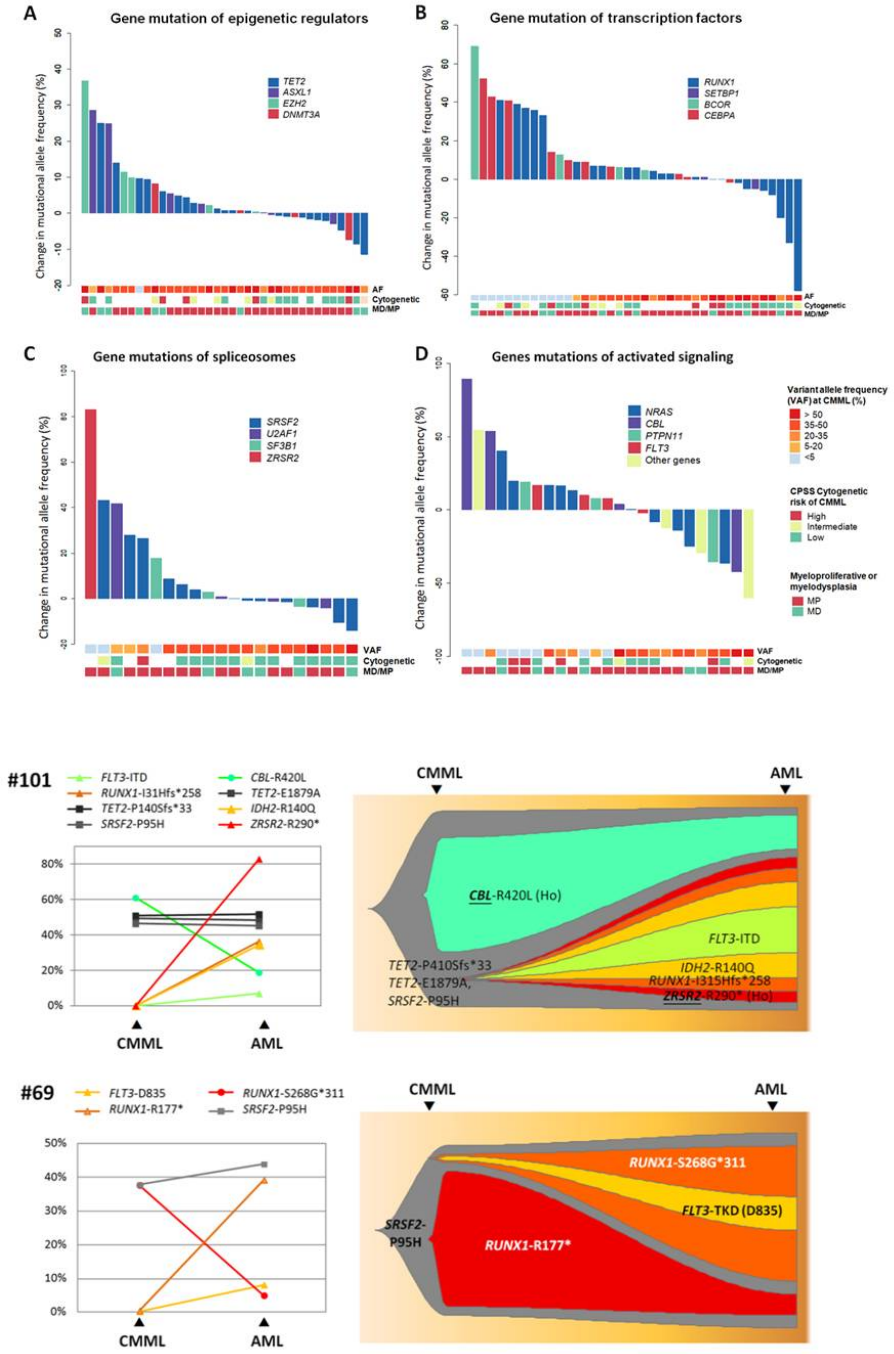
Between 1994 and 2021, 35 CMML patients with paired bone marrow samples in both CMML and sAML phases were examined. Mutational analyses including genes of epigenetic regulators, transcription factors, spliceosomes, activated signaling, cohesin complexes, *NPM1, WT1,* and *TP53* were performed. Gene mutations with variant allele frequency (VAF) were determined by pyrosequencing or next-generation sequencing. Zygosity was determined by VAF and SNP array. The clonal architecture of CMML/sAML patients was determined by VAF and the kinetics of VAF changes between CMML and sAML phases.

Results:

The median age of 35 patients was 67.8 (29.9-86.6) years at diagnosis of CMML. The median time to AML transformation was 14.7 (1.0-88.4) months. The most frequent gene mutations at the diagnosis of CMML were mutations in *RUNX1* (52.9%), *TET2* (46.9%), *SRSF2* (37.1%), and *ASXL1* (25.0%). The baseline VAF in epigenetic regulators was high (>35%) in 94.6% (35/37) of mutational events at the CMML phase, were constant in 81.1% (30/37, VAF changes <10%), and increased in 16.2% (6/37, increased VAF> 10%) during progression to sAML (Figure 1A). The baseline VAF in transcription factor genes was high (>35%) in 56.4% (22/39) of mutational events at the CMML phase, and remained stable in 64.1% (25/39) during sAML progression (Figure 1B). Acquisition of *RUNX1, CEBPA,* or *BCOR* mutations was frequent, and loss of *RUNX1*-mutated clones could be observed. The VAF in spliceosome genes was high (>35%) in 66.7% (14/21) of mutational events at the CMML phase, and remained stable in 61.9% (13/21) during sAML progression (Figure 1C). Genes involved in activated signaling were unstable with both acquisition and loss observed during sAML transformation (Figure 1D). *TET2* combined with *SRSF2* mutations (n=7) were the most frequent founder mutations in CMML. *RUNX1* mutations were usually a later event. *ASXL1* or *EZH2* mutations might occur earlier than *TET2* mutations. Acquisition of mutations in *CEBPA, IDH1/2,* inv(16)(p13.1;q22), or activated signaling genes including *FLT3, JAK2,* or *CBL*, could occur during sAML progression (Figure 2).

Summary/Conclusion:

A comparison of paired samples found that CMML was initiated from founding clones**,** and progressed by the acquisition of mutations through linear or branching evolution. The process of progression from CMML to sAML was complex and heterogeneous. This knowledge improves understanding of the clonal evolution from CMML to sAML and may help inform treatment strategies.



Keywords: Acute myeloid leukemia, Clonality, Adult, Chronic myelomonocytic leukemia