ASXL1 mutations in younger adult patients with acute myeloid leukemia: a study by the German-Austrian Acute Myeloid Leukemia Study Group.

Abstract:
We studied 1696 patients (18 to 61 years) with acute myeloid leukemia for ASXL1 mutations and identified these mutations in 103 (6.1%) patients. ASXL1 mutations were associated with older age (P<0.0001), male sex (P=0.041), secondary acute myeloid leukemia (P<0.0001), and lower values for bone marrow (P<0.0001) and circulating (P<0.0001) blasts. ASXL1 mutations occurred in all cytogenetic risk-groups; normal karyotype (40%), other intermediate-risk cytogenetics (26%), high-risk (24%) and low-risk (10%) cytogenetics. ASXL1 mutations were associated with RUNX1 (P<0.0001) and IDH2(R140) mutations (P=0.007), whereas there was an inverse correlation with NPM1 (P<0.0001), FLT3-ITD (P=0.0002), and DNMT3A (P=0.02) mutations. Patients with ASXL1 mutations had a lower complete remission rate (56% versus 74%; P=0.0002), and both inferior event-free survival (at 5 years: 15.9% versus 29.0%; P=0.02) and overall survival (at 5 years: 30.3% versus 45.7%; P=0.0004) compared to patients with wildtype ASXL1. In
multivariable analyses, ASXL1 and RUNX1 mutation as a single variable did not have a significant impact on prognosis. However, we observed a significant interaction (P=0.04) for these mutations, in that patients with the genotype ASXL1(mutated)/RUNX1(mutated) had a higher risk of death (hazard ratio 1.8) compared to patients without this genotype. ASXL1 mutation, particularly in the context of a coexisting RUNX1 mutation, constitutes a strong adverse prognostic factor in acute myeloid leukemia.