In this study, we evaluated the impact of secondary genetic lesions in acute myeloid leukemia (AML) with \(\text{inv}(16)(p13.1;q22)\) or \(t(16;16)(p13.1;q22)\); \(\text{CBFB-MYH11}\). We studied 176 patients, all enrolled on prospective treatment trials, for secondary chromosomal aberrations and mutations in \(\text{N-} /\text{KRAS}\), \(\text{KIT}\), \(\text{FLT3}\), and \(\text{JAK2} \ (\text{V617F})\) genes. Most frequent chromosomal aberrations were trisomy 22 (18%) and trisomy 8 (16%). Overall, 84% of patients harbored at least 1 gene mutation, with RAS being affected in 53% (45% \(\text{NRAS}\); 13% \(\text{KRAS}\)) of the cases, followed by \(\text{KIT}\) (37%) and \(\text{FLT3}\) (17%; \(\text{FLT3-TKD}\) [14%], \(\text{FLT3-ITD}\) [5%]). None of the secondary genetic lesions influenced achievement of complete remission. In multivariable analyses, \(\text{KIT}\) mutation (hazard ratio [HR] = 1.67; \(P = .04\)), \(\log(10)\) (WBC) (HR = 1.33; \(P = .02\)), and trisomy 22 (HR = 0.54; \(P = .08\)) were relevant factors for relapse-free survival; for overall survival, \(\text{FLT3}\) mutation (HR = 2.56; \(P = .006\)), trisomy 22 (HR = 0.45; \(P = .07\)), trisomy 8 (HR = 2.26; \(P = .02\)), age (difference of 10 years, HR = 1.46; \(P = .01\)), and therapy-related AML (HR = 2.13; \(P = .14\)) revealed as prognostic
factors. The adverse effects of KIT and FLT3 mutations were mainly attributed to exon 8 and tyrosine kinase domain mutations, respectively. Our large study emphasizes the impact of both secondary chromosomal aberrations as well as gene mutations for outcome in AML with inv(16)/t (16; 16).