Gene mutations and response to treatment with all-trans retinoic acid in elderly patients with acute myeloid leukemia. Results from the AMLSG Trial AML HD98B.

BACKGROUND: In a previous randomized trial, AML HD98B, we showed that administration of all-trans retinoic acid in addition to intensive chemotherapy improved the outcome of older patients with acute myeloid leukemia. The objectives of this study were to evaluate the prognostic impact of gene mutations and to identify predictive genetic factors for the all-trans retinoic acid treatment effect.

DESIGN AND METHODS: Data from mutation analyses of the NPM1, CEBPA, FLT3, and MLL genes were correlated with outcome in patients 61 years and older treated within the AML HD98B trial. RESULTS: The frequencies of mutations were: NPM1, 23%; CEBPA, 8.5% (analysis restricted to patients with a normal karyotype); FLT3 internal tandem duplications (ITD), 17%; FLT3 tyrosine kinase domain mutations, 5%; and MLL partial tandem duplications, 4.5%. The genotype mutant NPM1 was positively and adverse cytogenetics as well as higher white blood cell count negatively correlated with achievement of complete remission. In Cox regression analysis, a significant interaction between the genotype mutant NPM1 without...
FLT3-ITD and treatment with all-trans retinoic acid was identified, in that the beneficial effect of all-trans retinoic acid on relapse-free and overall survival was restricted to this subgroup of patients. Other significant factors for survival were age, adverse cytogenetics, and logarithm of white cell count. CONCLUSIONS: In elderly patients with acute myeloid leukemia, NPM1 mutations are associated with achievement of complete remission, and the genotype 'mutant NPM1 without FLT3-ITD' appears to be a predictive marker for response to all-trans retinoic acid given as an adjunct to intensive chemotherapy (ClinicalTrials.gov Identifier: NCT00151242).