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Mutation clearance after induction therapy in acute myeloid leukemia

After initial induction chemotherapy for acute myeloid leukemia, approximately 20 percent of patients fail to achieve complete remission, and approximately 50 percent experience relapse within one year. Therefore, it would be clinically useful to identify patients at higher risk of induction therapy failure or relapse. Recent studies have identified mutations in coding regions that have demonstrated significant prognostic value, but, to the authors' knowledge, no studies have examined mutations in noncoding regions. Furthermore, it may be beneficial to monitor the clearance of a patient's leukemia-associated mutations to assess response to therapy because the presence of persistent molecular disease may be associated with worse outcomes. The authors conducted a study in which they examined whole genome sequencing, exome sequencing, mRNA and microRNA sequencing, and methylation array data from 71 patients with acute myeloid leukemia. Three groups of patients were compared: those with refractory disease or who relapsed within six months of induction therapy, those who relapsed between six and 12 months after induction therapy, and those who maintained complete remission for more than 12 months. Overall, there was no significant difference in numbers of mutations or types of mutations among the groups, and this comprehensive genomic analysis yielded no independent prognostic information beyond the standard prognostic indicators currently in use. The authors then examined whether exome sequencing could be used to follow the presence of a patient's leukemia-associated mutations to determine molecular remission. Using samples from 50 patients who achieved morphologic remission at 30 days, exome sequencing was performed on the diagnostic marrow prior to induction therapy and on the marrow at day 30. Even though all 50 patients achieved morphologic remission, the clearance of the leukemia-associated mutations varied. Twenty-six of the patients completely cleared all leukemia-associated variants, while 24 had at least one mutation remaining after therapy. The patients with at least one persistent leukemia-associated variant showed significantly decreased event-free and overall survival rates. The number of persistent variants after therapy was not significantly associated with a shortened time to relapse. Overall, although no new biomarkers with independent prognostic information were discovered, the authors demonstrated the proof of concept that persistence of leukemia-associated variants at the 30-day bone marrow was associated with increased risk of relapse. Interestingly, many of the leukemia-associated variants observed in this study are not usually examined in the commonly used panels of genes that represent the subset of genes recurrently mutated in acute myeloid leukemia. Therefore, it may be beneficial to perform full exome sequencing to risk-stratify patients.

Klco JM, Miller CA, Griffith M, et al. Association between mutation clearance after induction therapy and outcomes in acute myeloid leukemia. *JAMA.* 2015;314(8):811–822.

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