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Post-azacitidine clone size predicts outcome of patients with myelodysplastic syndromes and related myeloid neoplasms

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Abstract:
Azacitidine is a mainstay of therapy for MDS-related diseases. The purpose of our study is to elucidate the effect of gene mutations on hematological response and overall survival (OS), particularly focusing on their post-treatment clone size. We enrolled a total of 449 patients with MDS or related myeloid neoplasms. They were analyzed for gene mutations in pre- (n=449) and post- (n=289) treatment bone marrow samples using targeted-capture sequencing to assess the impact of gene mutations and their post-treatment clone size on treatment outcomes. In Cox proportional hazard modeling, multi-hit TP53 mutation (HR, 2.03; 95% CI, 1.42-2.91; P<.001), EZH2 mutation (HR, 1.71; 95% CI, 1.14-2.54; P=.009), and DDX41 mutations (HR, 0.33; 95% CI, 0.17-0.62; P<.001), together with age, high-risk karyotypes, low platelet, and high blast counts, independently predicted OS. Post-treatment clone size accounting for all drivers significantly correlated with International Working Group (IWG)-response (P<.001, trend test), except for that of DDX41-mutated clones, which did not predict IWG-response. Combined, IWG-response and post-treatment clone size further improved the prediction of the original model and even that of a recently proposed molecular prediction model, IPSS-M (c-index, 0.653 vs 0.688; P<.001, likelihood ratio test). In conclusion, evaluation of post-treatment clone size, together with pre-treatment mutational profile as well as IWG-response have a role in better prognostication of azacitidine-treated myelodysplasia patients.

Conflict of interest: COI declared - see note

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