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**CD33 Splicing Polymorphism Determines Gemtuzumab Ozogamicin Response in De Novo Acute Myeloid Leukemia: Report From Randomized Phase III Children's Oncology Group Trial AAML0531.**

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**Abstract**

Purpose Gemtuzumab ozogamicin (GO), a CD33-targeted immunoconjugate, is a re-emerging therapy for acute myeloid leukemia (AML). CD33 single nucleotide polymorphism rs12459419 C>T in the splice enhancer region regulates the expression of an alternatively spliced CD33 isoform lacking exon2 (D2-CD33), thus eliminating the CD33 IgV domain, which is the antibody-binding site for GO, as well as diagnostic immunophenotypic panels. We aimed to determine the impact of the genotype of this splicing polymorphism in patients with AML treated with GO-containing chemotherapy. Patients and Methods CD33 splicing single nucleotide polymorphism was evaluated in newly diagnosed patients with AML randomly assigned to receive standard five-course chemotherapy alone (No-GO arm, n = 408) or chemotherapy with the addition of two doses of GO once during induction and once during intensification (GO arm, n = 408) as per the Children's Oncology Group AAML0531 trial. Results The rs12459419 genotype was CC in 415 patients (51%), CT in 316 patients (39%), and TT in 85 patients (10%), with a minor allele frequency of 30%. The T allele was significantly associated with higher levels of D2-CD33 transcript (  $P < 1.0E-6$ ) and with lower diagnostic leukemic cell surface CD33 intensity (  $P < 1.0E-6$ ). Patients with the CC genotype had significantly lower relapse risk in the GO arm than in the No-GO arm (26% v 49%;  $P < .001$ ). However, in patients with the CT or TT genotype, exposure to GO did not influence relapse risk (39% v 40%;  $P = .85$ ). Disease-free survival was higher in patients with the CC genotype in the GO arm than in the No-GO arm (65% v 46%, respectively;  $P = .004$ ), but this benefit of GO addition was not seen in patients with the CT or TT genotype. Conclusion Our results suggest that patients with the CC genotype for rs12459419 have a substantial response to GO, making this a potential biomarker for the selection of patients with a likelihood of significant response to GO.

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