

Potential biomarker for acute myeloid leukaemia therapy

Gemtuzumab ozogamicin, a CD33-targeted therapy for acute myeloid leukaemia (AML), significantly improves outcomes compared with standard chemotherapy in patients with a specific CD33 splicing polymorphism genotype, according to a recent study.

In the phase 3 Children's Oncology Group Trial AAML0531, 816 newly diagnosed patients with AML were randomised to receive either standard five-course chemotherapy (n=408) or chemotherapy plus two additional doses of 3 mg/m² gemtuzumab ozogamicin (n=408). In this report, Jatinder Lamba (University of Florida, Gainesville, FL, USA) and colleagues evaluated the patients for the presence of the CD33 splicing polymorphism—a single nucleotide polymorphism rs12459419 C>T in the splice enhancer region. The rs12459419 genotype was CC in 415

(51%) patients, CT in 316 (39%), and TT in 85 (10%). The minor (T) allele (frequency 30%) was associated with increased levels of the D2-CD33 isoform and with lower diagnostic leukaemic cell surface CD33 intensity.

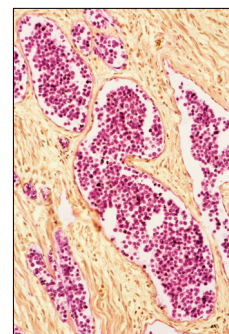
Patients with the CC genotype had a significantly lower relapse risk in the gemtuzumab ozogamicin group than in the chemotherapy-alone group (26% vs 49%; p<0.001), whereas this difference between treatments was not recorded in patients with the CT or TT genotype (39% vs 40%; p=0.85). Disease-free survival was also higher in patients with the CC genotype in the gemtuzumab ozogamicin group than in the chemotherapy group (65% vs 46%; p=0.004) but not in patients with the CT or TT genotype.

"We are excited as our results show a dramatic impact of an inherited genetic variation to predict gemtuzumab response at much greater level than

any of the known factors reported so far," explained Lamba. "This will allow us to personalise gemtuzumab therapy by pre-emptive genotyping to predict who will respond to the treatment (almost 50% of the AML patient population)...avoiding exposure to significant toxicity for patients who are not likely to respond, thus allowing for safe and effective use of gemtuzumab."

Martin Bornhäuser (University Hospital, Dresden, Germany) affirmed the positive impact on treatment approaches. "If confirmed in independent cohorts, this biomarker may be elegantly used to identify patients likely to benefit from the current anti-CD33 immunotherapies, at the same time sparing toxicity in others. Finally, it may stimulate the development of novel antibodies targeting alternative epitopes of CD33."

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For the study by Lamba and colleagues see *J Clin Oncol* 2017; published online June 23. <https://doi.org/10.1200/JCO.2016.71.2513>