High CD33 Levels on Pediatric Leukemic Blasts Predicts Poor Outcome

April 16, 2012

JR Schoenborn

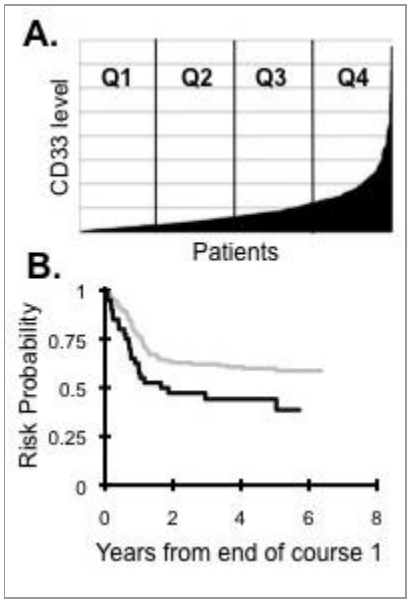
Most patients with acute myeloid leukemia (AML) express the myeloid antigen CD33 on the surface of leukemic blasts. CD33 is a transmembrane receptor that has been targeted for cytotoxic monoclonal-antibody-based therapy called gemtuzumab ozogamicin (GO or Mylotarg). With the goal of classifying the variability of CD33 expression with disease characteristics of childhood AML, Drs. Jessica Pollard and Soheil Meshinchi and colleagues in the CRD division have recently quantified CD33 levels on leukemic blasts obtained from 619 *de novo* childhood AML patients, and correlated these levels with the patients' biological and molecular disease features and clinical outcomes. The results show a strong association of high CD33 expression with adverse biological and molecular features of the disease and, with multivariate analysis, high CD33 expression is an independent predictor of poor outcome.

Normally, CD33 is expressed in early multilineage hematopoietic progenitors, but decreases as cells differentiate into myeloid or monocytic progenitors. Because AML blasts can derive from multiple points along myeloid differentiation, CD33 levels may reflect the differentiation or maturity of the leukemic progenitor. In addition, several prognostic cytogenetic and molecular features have been identified for AML. These include mutations in the tyrosine kinase-associate growth factor receptor FLT3, nucleolar phosphoprotein *NPM1* and the transcription factor *CEBPA*. High CD33 expression was associated with high-risk *FLT3/ITD* mutations and inversely associated with low risk disease *NPM1* mutations and *CBF* translocations. Elevated CD33 expression was also strongly correlated with poor disease-free and overall survival among patients. Finally, in several univariate and multivariate statistical models, high CD33 expression was a significant prognostic factor to predict poor outcomes.

On-going studies will examine if CD33 levels influence response to GO treatments. A recent phase 3 clinical trial with a head-to-head comparison of GO to conventional chemotherapy prompted the FDA to withdraw approval of GO as a standard AML therapy in 2010. However, GO may benefit a specific subgroup of AML patients, likely based on CD33 expression or other associated disease factors. Moreover, this work supports studies that examine GO's ability to improve outcomes for patients with low CD33 expression, a group that has previously been excluded from adult GO trials.

Finally, inclusion of CD33 levels into risk assessments of patients may further assist in assignment to risk stratified AML therapy that may include other CD33-targeting therapeutics.

Pollard JA, Alonzo TA, Loken M, Gerbing RB, Ho PA, Bernstein ID, Raimondi SC, Hirsch B, Franklin J, Walter RB, Gamis A, Meshinchi S. 2012. Correlation of CD33 expression level with disease characteristics and response to gemtuzumab ozogamicin containing chemotherapy in childhood AML. *Blood*. DOI:10.1182/blood-2011-12-398370.



Adapted from images provided by the authors.

CD33 expression on pediatric AML blasts is highly variable and correlates with disease-free survival. A) Distribution of CD33 expression for the 619 patients; B) Correlation of disease-free survival with CD33 expression (grey = lowest 3 quartiles, black = highest CD33 expression quartile).