AML score that combines genetic and epigenetic changes might help guide therapy

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(Medical Xpress)—Currently, doctors use chromosome markers and gene mutations to determine the best treatment for a patient with acute myeloid leukemia (AML). But a new study suggests that a score based on seven mutated genes and the epigenetic changes that the researchers discovered were present might help guide treatment by identifying novel subsets of patients.

The findings, published in the *Journal of Clinical Oncology*, comes from a study led by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James).

The epigenetic change used in the study is DNA methylation. It involves the addition of methyl groups to DNA, which can reduce or silence a gene's activity, or expression. Abnormal DNA methylation alters normal gene expression and often plays an important role in cancer development.

Overall, the findings suggest that patients with a low score – indicating that one or none of the seven genes is overexpressed in AML cells – had the best outcomes, and that patients with high scores – that is, with six or seven genes highly expressed – had the poorest outcomes.

"To date, disease classification and prognostication for AML patients have been based largely on chromosomal and genetic markers," says co-senior investigator Clara D. Bloomfield, MD, Distinguished University

Professor, Ohio State University Cancer Scholar and Senior Adviser.

"Epigenetic changes that affect gene expression have not been considered. Here we show that epigenetic changes in previously recognized and prognostically important mutated genes can identify novel patient subgroups, which might better help guide therapy," says Bloomfield, who is also the William Greenville Pace III Endowed Chair in Cancer Research at Ohio State.

The seven-gene panel was identified in 134 patients aged 60 and older with cytogenetically normal acute myeloid leukemia (CN-AML) who had been treated on Cancer and Leukemia Group B (CALGB)/Alliance clinical trials.

The researchers computed a score based on the number of genes in the panel that were highly expressed in patients' AML cells, and retrospectively tested the score in two groups of older patients (age 60 and up) and two groups of younger patients (age 59 and under).

Patients with a low score – indicating that one or none of the seven genes is overexpressed – had the best outcomes. Patients with high scores – that is, with six or seven genes highly expressed – had the poorest outcomes.

"For this seven-gene panel, the fewer highly expressed genes, the better the outcome," says co-senior author Guido Marcucci, MD, professor of medicine and the associate director for translational research at the OSUCCC – James. "In both younger and older patients, those who had no highly expressed genes, or had one highly expressed gene had the best outcomes."

Most adults with AML are not cured by current therapies. Only about 40 percent of patients younger than age 60 and about 10 percent of patients

60 and older are alive after three years, so new strategies for treating the disease and for matching the right patient with the right treatment are needed, Bloomfield says.

For this study, Bloomfield, Marcucci and their colleagues used next-generation sequencing to analyze regions of methylated DNA associated with prognostically important gene mutations in CN-AML cells from 134 patients aged 60 and older.

The seven genes identified by the researchers were CD34, RHOC, SCRN1, F2RL1, FAM92A1, MIR155HG and VWA8. For each of these genes, lower expression and higher DNA methylation were associated with better outcome. A summary score was developed based on the number of genes in the panel showing high expression. The researchers validated the score in four sets of patients: older and younger patients with primary AML, and older and younger patients with CN-AML (355 patients total).

When Bloomfield, Marcucci and their collaborators applied the unweighted score to the initial training set of 134 older patients, those with one or no highly expressed genes had a 96 percent complete-remission rate, 32 percent three-year disease-free survival rate and 39 percent three-year overall survival.

Patients with six-to-seven highly expressed genes, on the other hand, had a 25 percent complete-remission rate, a 0 percent three-year disease-free survival rate and 4 percent three-year overall survival.

For younger adult patients, those under age 60, those with one or no highly expressed genes had a 91-100 percent complete-remission rate, a 60-65 percent three-year disease-free survival rate, and a 76-82 percent three-year overall survival. Patients with six-to-seven highly expressed genes, on the other hand, had a 53-71 percent complete-remission rate, a

13-17 percent three-year disease-free survival rate and a 7-24 percent three-year overall survival.

"Overall, our findings suggest that the unweighted-summary score is a better model compared with all other prognostic markers and previously reported gene-expression profiles," Bloomfield says.

More information: "Epigenetics Meets Genetics in Acute Myeloid Leukemia: Clinical Impact of a Novel Seven-Gene Score." Guido Marcucci, Pearlly Yan, Kati Maharry, David Frankhouser, Deedra Nicolet, Klaus H. Metzeler, Jessica Kohlschmidt, Krzysztof Mrózek, Yue-Zhong Wu, Donna Bucci, John P. Curfman, Susan P. Whitman, Ann-Kathrin Eisfeld, Jason H. Mendler, Sebastian Schwind, Heiko Becker, Constance Bär, Andrew J. Carroll, Maria R. Baer, Meir Wetzler, Thomas H. Carter, Bayard L. Powell, Jonathan E. Kolitz, John C. Byrd, Christoph Plass, Ramiro Garzon, Michael A. Caligiuri, Richard M. Stone, Stefano Volinia, Ralf Bundschuh, and Clara D. Bloomfield. *Journal of Clinical Oncology*. 2013.50.6337; published online on December 30, 2013; DOI: 10.1200/JCO.2013.50.6337

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