Discovery of genetic mutations better diagnose myelodysplastic syndromes

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For patients with myelodysplastic syndromes (MDS), choosing the appropriate treatment depends heavily on the prognosis. Those patients at the highest risk of dying from their disease are typically offered the most aggressive therapies, while patients at lower risk could live several years with MDS, needing only supportive care or other relatively side-effect free treatments. While some clinical variables are useful, current methods for predicting prognosis for individual patients are not ideal. Patients with the same clinical features can have very different outcomes from their disease. Researchers at Brigham and Women's Hospital (BWH) have developed a means of improving prognosis methods and predicting how long patients with MDS will live after diagnosis by identifying certain gene mutations in their abnormal bone marrow. These findings are published in the June 30 issue of the *New England Journal of Medicine*.

MDS is a cancer of the bone marrow and blood that can range in severity and likelihood to progress to acute leukemia. For patients with related diseases, such as acute myeloid leukemias or myeloproliferative disorders, single gene mutations are commonly used to make diagnoses, predict outcomes, and track disease burden. "Information about gene mutations is not used clinically at the moment for patients with MDS," noted Benjamin Levine Ebert, MD, PhD, at BWH. "In particular, using these mutations to determine the prognosis of patients can help dictate appropriate treatment for patients based on the current state of the disease."

The researchers used a combination of genomic approaches, including next-generation sequencing and mass spectrometry–based genotyping, to identify mutations in samples of bone marrow from 439 patients with MDS. They then examined whether the mutation status for each gene was associated with clinical variables and overall survival.

Clinicians currently use scoring systems to classify MDS patients into different risk groups based on clinical features of their disease, but mutations in individual genes are not currently used. Some patients currently predicted to have low risk disease progress rapidly. "In this study we identified mutations in several genes that predict a worse prognosis for patients than we would have expected using the most commonly used clinical scoring system (the International Prognostic Scoring System for MDS, or IPSS)," said Dr. Ebert.

Nearly a third of the patients in this study were found to have mutations in one or more of the five prognostic genes identified. If physicians knew that one of their low risk patients had such a mutation, they might decide to offer them more aggressive treatment or monitor them more closely.

Prior studies have suggested that mutations in individual genes can change the predicted prognosis of patients in MDS, but often included only a small number of patients or only considered mutations in a few genes. This study is the first to examine a large number of genes in such a large group of patients, allowing the researchers to determine how frequently mutations in different genes occurred and how often they overlapped with each other. This also allowed them to determine which mutations were the most important independent predictors of prognosis.

Moving forward, researchers hope to identify mutations that predict response to individual therapies. They expect that this genetic information will be used clinically as part of a novel prognostic scoring

system and as predictors of therapeutic responses. This will allow us to further individualize the care of patients with MDS.

Provided by Brigham and Women's Hospital