APC Sepsis Prevention Not Linked to Anticoagulant Effects

James M. Coghill, MD,
and Alice Ma, MD

For adult patients with acute myeloid leukemia (AML), disease karyotype is the strongest predictor of long-term outcome. Current prognostic schemes broadly assign patients to one of three risk categories based on the presence or absence of large chromosomal abnormalities such as t(8;21), t(15;17), deletion 16, monosomy 7, and complex aneuploidy. Most patients present with an apparently normal karyotype and are therefore grouped together in the "intermediate" risk category. In reality such patients represent a considerably heterogeneous population with often unpredictable clinical courses. There has consequently been much interest in exploring more subtle molecular markers that can be used to estimate disease prognosis and guide therapy.

At yesterday's Plenary Scientific Session, Dr. Richard F. Schlenk presented "Gene Mutations as Predictive Markers for Postremission Therapy in Younger Adults with Normal Karyotype AML." These exciting new data may allow for a more tailored therapeutic approach to such patients. Dr. Schlenk's group registered 872 patients with normal karyotype AML from four AMLSG treatment trials and obtained tumor samples from most. Several genes were examined for mutations including: NPM1, FLT3 (FLT3-ITD and FLT3-TKD), CEBPA, MLL (PTD), and NRAS. Using a logistic regression model, two mutation combinations were identified as predicting response to induction therapy: $NPM1^+/FLT3\text{-}ITD^-$ and $CEBPA^+$. Cox proportional hazard models were then constructed to identify prognostic factors for relapse-free (RFS) and overall survival (OS). Age < 48 years, the availability of a matched-related donor (MRD), and in particular the $NPM1^+/FLT3\text{-}ITD^-$ (hazard ratio (HR) 0.34 and 0.43 for RFS and OS survival respectively) and $CEBPA^+$ genotypes (HR 0.42 and 0.36), were all associated with improved outcomes. Interestingly, in those patients with the $NPM1^+/FLT3\text{-}ITD^-$ genotype combination, the availability of a MRD did not appear to confer a significant survival advantage (HR 0.89 and 0.93 for RFS and OS respectively). In contrast, for those patients possessing all other combinations of NPM1 and FLT3-ITD, four-year RFS was significantly higher in those with a MRD (47 percent) versus those without a donor (23 percent). This implies that allogeneic hematopoietic stem-cell transplantation (HSCT) in first complete remission (CR) does offer benefit over standard post-remission therapy in normal karyotype AML, but only in those without the $NPM1^+/FLT3\text{-}ITD^-$ genotype.

Dr. Schlenk's study is groundbreaking in that it simultaneously included multiple genetic markers in its prognostic modeling. The hazard ratios for the $NPM1^+/FLT3\text{-}ITD^-$ and $CEBPA^+$ genotypes are particularly impressive and appear to strongly predict a subset of normal karyotype patients destined for good clinical outcomes. Although the model will ultimately require prospective validation, it appears to provide a new tool with which hematologists can identify those most likely to benefit from upfront allogeneic HSCT and spare good-prognosis patients from unnecessary transplant-related morbidity. Such an approach may allow for more individualized therapy in the near future.