Investigation of Markers Which Reliably Predict for Disease Progression in Patients with Chronic Lymphocytic Leukemia

Kendra L. Yale, (Margaret Yu)
Huntsman Cancer Institute, University of Utah

By following the expression of Zap-70, a marker which correlates well with unmutated immunoglobulin genes and an aggressive form of chronic lymphocytic leukemia (CLL), in patients with CLL, we have been able to show by Western blot assay that the presence of Zap-70 disappears after treatment. Although we have received optimal results in a number of cases, Zap-70 measurements are not always consistent.

The continuation of this project will focus on our hypothesis that a combination of Zap-70 expression and DNA methylation levels will better predict for early disease progression in patients with CLL.

We know that DNA is abnormally methylated in patients with CLL, and based on preliminary data from 22 patients, we propose that patients with high methylation levels (> 3.8%) have disease progression and those with low methylation levels (< 3.8%) have a less aggressive form of the disease. We will perform a comparative analysis of Zap-70 to DNA methylation in 100 newly-diagnosed patients with CLL to determine if those with higher methylation levels with or without Zap-70 expression require treatment sooner than patients with low methylation levels. We will check for Zap-70 by immunochemistry and flow cytometry. DNA methylation levels in the peripheral blood leukocytes will be measured by high performance liquid chromatography after DNA digestion. Mutational status of immunoglobulin variable genes will also be performed.

By understanding the extent to which methylation levels relate to the aggressiveness of CLL, we may be able to use methylation inhibitors in the treatment of this disease. Methylation inhibitors re-express genes previously silenced by DNA methylation so normal cell function can occur. If we can identify the subset of patients who will benefit from treatment with a DNA methylation inhibitor, this may maintain CLL in a chronic state and prevent patients from having to endure the toxicity of chemotherapy.