Chronic Lymphocytic Leukemia Prognostic Markers

Indications for Ordering

Use to determine risk group in newly diagnosed chronic lymphocytic leukemia (CLL)

- IGHV mutation
- CD38 expression

Test Description

- IGHV Mutation Analysis by Sequencing
  - Polymerase chain reaction/sequencing using VH leader and JH primers
  - Identified clonal VH sequences are searched against a known database for homology
    - Percent of homology to germline sequences is reported
  - CLL clones comprising at least 50% of total B cells can be analyzed
- Leukemia/Lymphoma Phenotyping by Flow Cytometry
  - CD38 expression

Tests to Consider

Primary tests

- IGHV Mutation Analysis by Sequencing 0040227
  - Determine risk group in newly diagnosed CLL
- Leukemia/Lymphoma Phenotyping by Flow Cytometry 2008003
  - Aid in evaluation of hematopoietic neoplasms
  - Expression of CD38 typically performed for CLL diagnosis and followup

Related tests

- Cytophenic SNP Microarray – Oncology 2006325
  - Preferred test at time of diagnosis for detecting prognostically important genomic abnormalities in leukemias/lymphomas and solid tumors involving
    - Loss/gain of DNA
    - Loss of heterozygosity (LOH)
  - Monitor disease progression and response to therapy
- Chromosome FISH, CLL Panel 2002295
  - Alternate test to detect prognostically important genomic abnormalities in CLL
    - Not as sensitive as SNP microarray
  - Includes ATM (11q22.3), chromosome 12 centromere (Trisomy 12), (D13S319) 13q14.3, p53 (17p13.1)

Results

IGHV mutation

- Nonmutated VH segment
  - >98% identical to the most closely matched germline VH gene sequence
  - Associated with unfavorable outcome
- Mutated VH segment
  - <98% identical to the most closely matched germline VH gene sequence
  - Associated with favorable outcome
  - Borderline mutation
    - 97-97.9% identical to the most closely matched germline VH gene sequence
    - May have an intermediate clinical outcome (Hamblin TJ, Br J Hematology, 2008)
- Expression of VH3-21 segment typically has an unfavorable outcome regardless of mutation status

CD38 expression

- Associated with unfavorable outcome

Disease Overview

Treatment issues

- CLL is a heterogenous disease
  - Therapy based on risk group stratification
  - Clinical course is variable
    - ~1/2 are aggressive, others are indolent
- Cytogenetic, molecular, and flow cytometry testing play an important role in prognostication of CLL

Significance of markers

- IGHV
  - IGHV mutation status of CLL tends to remain constant over course of disease
  - del(17p) and/or del(11q) correlate with nonmutated IGHV genes
  - Presence of mutation associated with more indolent course
- CD38 expression
  - Transmembrane glycoprotein modulates intracellular signaling
  - Cases that express CD38 often have nonmutated IGHV genes
  - May reflect an increased proliferative status of CLL
  - Expression levels may vary over course of disease
Limitations

*IGHV* mutation

- Samples that do not yield amplification product may
  - Contain too few CLL cells (<50% B cells)
  - Express *VH* genes with high numbers of mutations that may compromise clonal B-cell amplification
- Not intended to detect minimal residual disease