

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma and Myeloma

Section Editor: Clara D. Bloomfield, MD

The Use of Molecular Markers in Selecting Therapy for CLL

Hartmut Döhner, MD
Professor of Medicine
Medical Director
Department of Internal Medicine III
University of Ulm

H&O What molecular markers are recognized in chronic lymphocytic leukemia to be related to prognosis?

HD In considering risk assessment based on genetics in chronic lymphocytic leukemia (CLL), there are 2 categories to consider. The first category is the so-called mutation status of the immunoglobulin variable (VH) genes. Two major subgroups of CLL have been defined based on the VH mutation status: mutated and unmutated. Drs. Terry Hamblin and Freda Stevenson, from the United Kingdom, and Dr. Chiorazzi, from New York, showed that the mutational status of these VH genes has an enormous impact on the prognosis of CLL patients: Those with mutated VH genes have a significantly better survival than those with unmutated VH genes.

The second category is specific chromosomal abnormalities. In a seminal paper published 4 years ago in the *New England Journal of Medicine*, we described a study showing that it is possible to subdivide CLL patients into prognostic subgroup based on their specific chromosomal abnormalities. The most frequently observed abnormalities are deletions of 13q, 11q, 17p, or trisomy 12. In this analysis, we showed that patients with 13q deletions as a single chromosomal abnormality have the best survival. Patients with trisomy 12 do worse, but still have an overall survival of over 10 years. High-risk karyotypes include deletions of 11q, associated with a median survival of 6–7 years, and deletions of 17p, associated with a median survival of approximately only 3 years.

H&O Are all CLL patients profiled for these molecular markers?

HD No. This type of genetic profiling is still considered a rather specialized molecular diagnostic tool. I would estimate that only a minority of patients is currently profiled, the highest proportion being those patients enrolled in prospective clinical trials. Ongoing studies being conducted by the Eastern Cooperative Oncology Group among others in the United States, the Medical Research Council in the United Kingdom, and by the German CLL group are obtaining data on molecular markers for all patients that enroll.

H&O What are the approximate percentages of patients in each subgroup you mentioned?

HD Approximately 40% of CLL patients have mutated VH genes, and approximately 60% do not. Using a hierarchical model to look at the chromosomal abnormalities, 13q deletion as a single abnormality occurs in approximately 35% of patients; 11q deletion in approximately 16%, trisomy 12 in approximately 14%, and 17p deletion in approximately 6%.

H&O Could you further describe the hierarchical model to which you are referring?

HD This hierarchical model is derived from a multivariate analysis with overall survival as the endpoint. Patients with 17p deletions, who do the worst, comprise the first subgroup. In the second subgroup are patients who do not have the 17p deletion, but have the 11q deletion, which is not as bad as 17p, but is worse than the others. In the third category are the trisomy 12 patients who do not exhibit a 17p or 11q deletion. The last subgroup is the 13q deletion as a single abnormality.

Of course, patients may have more than 1 chromosomal abnormality, but they can still be included in one of these subgroups.

H&O Do all CLL patients exhibit these abnormalities?

HD It is possible to detect abnormalities in approximately 80% of CLL patients. Thus, there are still 20% of patients

in whom it is not possible to detect any abnormalities with the methodology we are currently using.

H&O Is there a correlation between the mutation status or chromosomal abnormality and the therapy most likely to benefit a patient?

HD This is a huge topic, and I think it is important to be very conservative and not draw conclusions too quickly regarding therapy. Most of the data that we have right now are based on retrospective analyses. The first data from prospective studies will be available soon, and these data are needed in order to be sure that the findings of the retrospective analyses are being confirmed. That being said, we are beginning to obtain some initial understandings about the relationship between molecular markers and therapy.

As one example of the potential therapeutic application, it has been observed that for patients with the 17p deletion, no therapy has been successful. These patients do not respond to standard chemotherapy with chlorambucil (Leukeran, GlaxoSmithKline) or other alkylating agents, nor to fludarabine (Fludara, Berlex) or single-agent rituximab (Rituxan, Genentech/IDEC). However, these patients do respond to alemtuzumab (Campath-1H, Berlex). This finding is being confirmed in 2 larger studies. Therefore, for patients with the 17p deletion, it may be useful to treat the patient with alemtuzumab earlier than is usually done.

Here is another example. Approximately 2 years ago, we decided that younger CLL patients (under age 65) who have a poor prognostic marker would be eligible for allogeneic stem cell transplantation for first-line treatment using a nonmyeloablative conditioning regimen. The use of a molecular marker to stratify therapy is a very recent development. This approach is being evaluated prospectively in a clinical trial in Germany, as well as in studies in Spain and the United Kingdom.

H&O So is it possible that profiling patients according to these molecular markers will eventually lead to improved outcomes?

HD Having information from molecular diagnostics does not mean that treatment can be improved. This improvement may occur for patients with 17p deletions or for younger patients who undergo allogeneic stem cell transplantation, as discussed above. However, this improvement does not apply for the majority of patients having CLL. We do not yet know whether one treatment is more beneficial than another for any particular subgroup. This possibility is being explored in large prospective trials in which investigators are trying to evaluate whether patients with a specific abnormality benefit from a specific type of

treatment. Do patients with 11q deletion benefit particularly from treatment with immunochemotherapy using, for example, a regimen of fludarabine, cyclophosphamide, and rituximab? We do not yet know, but clinical trials are trying to find out.

Ultimately, the goal with the research of molecular markers in CLL is to understand what is going on in terms of cell signaling and cell cycle, so that drugs that interact with the signaling pathways associated with the specific abnormality can be developed.

H&O Is there a concern that clinicians are incorporating information about molecular markers into treatment considerations without proper data?

HD Yes, this is a concern. There is a trend right now for doctors to do this type of molecular profiling and, if a patient has one of the poor prognostic markers, to then start therapy immediately. There is no rationale to date to draw this conclusion. We do not know whether an earlier start of treatment with an intensive protocol does any benefit to CLL patients. This hypothesis should be part of a prospective trial, but right now, it is too early to make a change in clinical practice to incorporate molecular markers into the decision of the treatment approach.

H&O Could incorporating molecular markers into the decision-making process lead to harm of CLL patients?

HD Yes. There is no justification for treating an early-stage CLL patient based on the presence of a high-risk genetic marker. Intense treatment regimens that are increasingly used in this setting may be associated with increased morbidity and mortality. Evaluation of early intense therapy for high-risk patients should be restricted to clinical trials. Treatment decisions should still be based on very conventional criteria. These guidelines were published in 1998 and include B symptoms, night sweat, fever, rapidly growing lymph nodes, short lymphocyte double time, and other measures. These parameters should form the basis of our decisions on when and how to treat patients.

Suggested Reading

Stilgenbauer S, Dohner H. Molecular genetics and its clinical relevance. *Hematol Oncol Clin North Am.* 2004;18:827-848.

Krober A, Seiler T, Benner A, et al. V(H) mutation status, CD38 expression level, genomic aberrations, and survival in chronic lymphocytic leukemia. *Blood.* 2002;100(4):1410-1416.

Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in patients with chronic lymphocytic leukemia. *N Engl J Med.* 2000;343:1910-1916.