

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Minimal Residual Disease and Survival in Chronic Lymphocytic Leukemia

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H&O What is the rationale for measuring minimal residual disease?

PH Until 5 or so years ago, there were not many available therapies that would completely eradicate detectable disease in patients with chronic lymphocytic leukemia (CLL). The current internationally accepted response criteria are those set by the National Cancer Institute (NCI) in 1996, before the most recent therapies were developed. The definition of a complete remission (CR) is quite permissive: patients have to achieve a normal physical examination, resolution of symptoms, and relative normalization of blood counts. There is no requirement for imaging—whether abnormal lymph nodes can be detected by computed tomography scans, for example—and while normal-looking bone marrow is required, there is no requirement to look for low levels of CLL by any other test. A patient in remission could therefore have 2% or more CLL cells in the marrow yet still have a normal-looking marrow and thus be classified as a CR.

As one might expect, in most of the series for a variety of therapies, patients who achieved a CR survived better than patients who achieved a partial remission or no response. But many patients treated with chemotherapy were still relapsing and eventually dying from the disease despite the fact that they achieved a CR. There was no evidence, using the current definition of CR, that we were achieving prolonged remissions, and we were certainly not curing any patients.

It became clear that CLL patients who relapsed from residual disease still had disease in the marrow after their initial treatment, even when that treatment had put them

into remission. Investigators hypothesized that if the disease could be eradicated to a greater extent, then remission, and potentially survival, could be prolonged.

In addition, in the mid 1990s, when alemtuzumab (Campath, Berlex) was initially used for treating refractory CLL, we saw some patients who achieved a CR by conventional criteria, meaning that the bone marrow looked normal, and this finding triggered the development of assays to detect very low levels of disease.

H&O How is minimal residual disease measured?

PH Detecting minimal residual disease (MRD) requires a quantitative technique that will pick up extremely low levels of CLL. Also, such a technique should, ideally, provide immediate results: if a treatment regimen is being used in which the duration depends on the quality and depth of remission, then results are needed from diagnostic tests right away.

The 2 main approaches are polymerase chain reaction (PCR)-based diagnostics (molecular), which rely upon detection of the CLL clone-specific rearranged immunoglobulin gene, and flow cytometry, which looks at the “fingerprint” of antigens on the surface of CLL cells. This fingerprint looks different from that of normal cells, and therefore enables identification of the pattern of antigen expression and thus separation from normal B cells and normal cells in general.

One of the major disadvantages with PCR is that the sequence of the immunoglobulin gene rearrangement is different in each person, thus requiring specific sequencing of each individual patient's genes and then production of probes specific for those genes. This approach is quite laborious, time consuming, and expensive, and is not possible for every patient. Therefore, even though PCR is very sensitive as a real-time test, it is difficult to use.

By contrast, flow cytometry is generally easier to use, because every patient has the same immunophenotype regardless of how aggressive his or her disease may be. A single test will differentiate CLL cells from normal polyclonal B cells in all patients. One of the major advances in flow cytometry in the past 5–10 years is that this technology can now analyze larger numbers of cells more quickly, and can look at several different antigens on each cell at

the same time; the most recently developed assays can detect up to 6 or more antigens at a time. This advancement gives this type of analysis much more power, and the results are provided the same day or the day after, enabling its use in defining duration of therapy.

Right now, flow cytometry is the standard technique for analyzing MRD. When done well, PCR is somewhat more sensitive than flow cytometry, but the difference is not significant enough to make it the standard technique.

H&O Is the flow cytometry approach to detecting MRD accessible to all clinicians treating CLL?

PH Using flow cytometry to measure MRD is certainly feasible in all places that treat hematologic malignancies, since there would already be a flow cytometry laboratory in place for diagnostic purposes. The technique for detecting MRD is somewhat more complicated, so it may take some time to become comfortable with the test, but all the equipment and expertise should be available.

H&O Could you discuss the findings of your recently reported study evaluating B-cell CLL patients treated with alemtuzumab? What was the connection between MRD and survival?

PH We reported the findings of what was actually a series of sequential trials, the first of which was begun in 1996, with the ensuing studies completed in May 2003. The report, published recently in the *Journal of Clinical Oncology*, included data for all patients enrolled from 1996 through May 2003. The patients enrolled in these studies all had relapsed or refractory B-cell CLL, and were treated with alemtuzumab.

Within these studies, the aim of the treatment was to achieve a level of disease of below 1 in 10,000 or even 1 in 50,000 CLL cells. We reported on 91 patients with relapsed or refractory B-cell CLL who were treated with this intent. Of these patients, 18 achieved MRD negativity after treatment with single-agent alemtuzumab, with no detectable disease in the marrow. An additional 6 patients achieved an MRD(-) remission with alemtuzumab in combination with fludarabine (Fludara, Berlex) (n=2) or following a transplant using cells harvested after alemtuzumab treatment (n=4). Thus, just over one quarter of patients achieved an MRD(-) remission in the bone marrow at the end of treatment. In the published report, we showed that the most important predictor of survival was an MRD(-) remission. Of the 18 patients who achieved MRD negativity from single-agent alemtuzumab, the 5-year overall survival was greater than 80%, far more than would be expected with conventional treatment. Treatment-free survival for the MRD(-) patients was approximately 75% at 5 years.

H&O Was it noteworthy that these were relapsed/refractory patients? How do the findings compare to historical data?

PH Approximately half were refractory by conventional criteria, meaning they had failed to respond to prior fludarabine therapy. The majority of the remaining patients on this study had relapsed fairly quickly after having received fludarabine-based therapy. Based on historical data, we would expect that patients who are refractory to fludarabine would have a median survival of less than 1 year and a 5-year survival of 10%.

It is important to note that we were trying to achieve an MRD(-) remission in all patients, but this level of response only occurred in one quarter of patients. One possible explanation for the improved survival of patients achieving an MRD(-) remission is that these were a subgroup of patients who had a biologically better risk disease and therefore would have done better whether or not they had achieved that level of response. However, as the expected 5-year overall survival for refractory patients is approximately 10%, it appears highly unlikely that these patients would have done as well had they not achieved an MRD(-) remission.

To evaluate this question further, several groups are now considering conducting a trial in which patients would be randomly assigned to receive consolidation with alemtuzumab or not. There is one study planned for the UK that we hope will start in a year or so. Investigators in Germany have previously reported a similar trial with a small number of patients that is showing a benefit for the alemtuzumab arm. This trial demonstrated that an improvement in progression-free survival would be expected but that a better-tolerated alemtuzumab regimen needed developing.

H&O Is alemtuzumab the only agent for CLL that appears to eradicate the disease to the level of MRD negativity?

PH No, there are other therapeutic approaches that may result in MRD negativity. Certainly patients who have undergone allogeneic transplantation have a high probability of obtaining an MRD(-) status. Increasingly, there are reports about combinations of chemotherapy that may achieve an MRD(-) response. A Spanish group has reported that a quarter of patients appear to achieve MRD(-) remissions with the combination of fludarabine, cyclophosphamide, and mitoxantrone (FCM) given as first-line therapy. Combinations of antibodies and chemotherapy, such as fludarabine, cyclophosphamide, and rituximab (Rituxan, Genentech/Biogen Idec) (FCR), may produce MRD(-) remissions, but no such studies have been conducted thus far.

Autologous transplantation may also result in MRD(-) status, but, because the marrow has to be clear beforehand, MRD negativity is not necessarily entirely due to the transplantation itself.

At the present time, alemtuzumab is the only single agent in CLL that appears to be capable of eradicating detectable MRD in a significant proportion of patients.

H&O Do you envision these findings impacting future response criteria definitions?

PH Yes. The response criteria definitions are currently being rewritten. There have been meetings over the last 12 months involving representatives from the NCI and with the International Workshop on CLL (IWCLL). In September, there is a meeting of the IWCLL in the United States at which a day will be dedicated to reviewing response criteria. One of the main changes in the response criteria will be to incorporate MRD assessment for at least a proportion of the patients who are being treated with the intent of eradicating detectable MRD. In addition, we have been meeting with labs from around the world in an effort to standardize MRD detection techniques in order to ensure that MRD(-) remissions in one country are the same as MRD(-) remissions in another country. We are currently standardizing this approach and recommending the most effective test, which will also be reported at the IWCLL meeting. Most likely, revised response criteria will be available in early 2006 and will include an MRD assessment as part of the requirements for CR.

H&O Do these findings definitively establish that achieving MRD does indeed correlate with prolonged overall survival?

PH All of the patient series that have been published—autologous transplants, FCM, FCR—demonstrate that there is a prolongation of survival among the MRD(-) responders. In my estimation, these findings conclusively show that achieving an MRD(-) remission does predict for survival. However, what the findings do not show is whether achieving an MRD(-) remission is the endpoint that should be the target for all patients. It may be that good-prognosis patients achieve an MRD(-) remission,

and so this level of remission is simply a marker of a patient with a good prognosis. In order to verify the importance of achieving an MRD(-) remission, a clinical trial is needed that will compare an attempt to achieve MRD negativity versus just standard therapy. I think that the evidence is fairly convincing that MRD negativity will be an appropriate endpoint, at least for poor-risk CLL.

H&O What greater trends in CLL management are at play in studies such as the one you reported in the *Journal of Clinical Oncology*?

PH In the management of hematologic malignancies, and probably in oncology in general, the application of genetic factors and MRD assessment by flow cytometry is becoming an essential part of practice. As clinicians, we need to be aware of the implications of all these tests and to be sure that we have access to them so that they can be incorporated into treatment decisions.

This trend in CLL mirrors similar trends in the management of chronic myeloid leukemia and acute leukemias, and also in the increasing use of prognostic markers, such as fluorescent in situ hybridization. The entire field is shifting, especially over the past 5 years, toward therapy that is more tailored to the individual patient. We are increasingly moving toward patient-specific therapies in the treatment of leukemia and lymphoma that better enable us to provide the best treatment possible.

Suggested Reading

Moreton P, Kennedy B, Lucas G, et al. Eradication of minimal residual disease in B-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with prolonged survival. *J Clin Oncol*. 2005;23:2971-2979.

Hale G, Rebello P, Brettman LR, et al. Blood concentrations of alemtuzumab and antiglobulin responses in patients with chronic lymphocytic leukemia following intravenous or subcutaneous routes of administration. *Blood*. 2004;104:948-955.

Rawstron AC, Kennedy B, Evans PA, et al. Quantitation of minimal disease levels in chronic lymphocytic leukemia using a sensitive flow cytometric assay improves the prediction of outcome and can be used to optimize therapy. *Blood*. 2001;98:29-35.

Botthcher S, Ritgen M, Pott C, et al. Comparative analysis of minimal residual disease detection using four-color flow cytometry, consensus IgH-PCR, and quantitative IgH PCR in CLL after allogeneic and autologous stem cell transplantation. *Leukemia*. 2004;18:1637-1645.

Bruggemann M, Pott C, Ritgen M, Kneba M. Significance of minimal residual disease in lymphoid malignancies. *Acta Haematol*. 2004;112:111-119.