Scientific & Clinical

The role of Freelite™ and Hevylite™ serum assays in myeloma

Myeloma Today in conversation with Dr. Brian G.M. Durie

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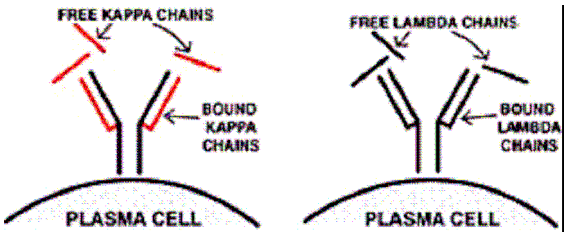
Would you please bring us up to date on the use of Freelite™ serum free light chain assays in multiple myeloma?

For several years now, Freelite™ serum free light chain assays, which measure free lambda and free kappa immunoglobulin light chains, have been used for the detection of oligosecretory (sometimes called "non-secretory") multiple myeloma and for assessment of patients with MGUS (monoclonal gammopathy of undetermined significance), as well as for monitoring disease progression and for evaluating treatment response in these patients. Patients with oligosecretory myeloma do not have the typical M protein spike in either blood or urine, and Freelite has been an effective tool in diagnosing and monitoring such patients.

Is Freelite also applicable to myeloma patients who have the M spike?

This potential application of Freelite is still being explored. For example, baseline levels of Freelite have prognostic significance with higher levels indicating more aggressive disease. Freelite is currently used as part of myeloma clinical trials being conducted in different settings, and we hope that the data will clarify the utility of Freelite in patients who are not oligosecretory. In other words, if a myeloma patient has a regular M component, it is the spike that should be measured and monitored. However, with the introduction of novel anti-myeloma therapies, more and more patients are having a complete response (CR) or a very good partial response (VGPR) assessed using the serum and/or urine M component. When patients have a very low level of disease, they

still have low levels of measurable free light chains. So the question we are now addressing is the utility of Freelite for quantitative assessment of minimal residual disease. It is useful to apply Freelite for monitoring in this setting. For example, this test gives an earlier indication of disease relapse.



When immunoglobulin molecules are produced by the plasma cells in the bone marrow, the heavy chains (G, A, M, D, or E) and the light chains (kappa or lambda) are produced separately. The kappa and lambda molecules are bound to the heavy chains and intact immunoglobulins are assembled, then transported to the surface of the plasma cell. Free kappa and lambda light chains are produced in excess, and the Freelite test quantifies the free kappa and free lambda light chain concentrations.

Are there pros and cons to using Freelite to assess minimal residual disease?

It is useful because we can get some measurable numbers. But, at the very low levels of free light chains, there is fluctuation and this up and down bounce can be disconcerting to patients and physicians alike. So it is important for patients to keep in mind that they are being monitored at such low levels of disease that, even with the numbers fluctuating, the test results are usually way below where one needs to take any action.

The key question is what are the situations where such monitoring is actually useful? One example of this is the normalization of the Freelite Ratio in a responding patient – when a patient has a normal serum or urine spike plus the Freelite ratio tests as normal. This is part of the definition of stringent CR (sCR) – the absence of the M spike, the immunofixation is negative, the bone marrow is normal, and the Freelite ratio is normal. This is a definitive endpoint which is part of the International Myeloma Working Group (IMWG) uniform response criteria and now being prospectively evaluated as part of ongoing trials.

So how is Freelite being used in the ongoing myeloma clinical trials?

In all the different protocols and trials, the studies are looking at the differences between sCR and CR with an abnormal Freelite Ratio. Freelite might turn out to be the best way to identify best reponse, but there is no final answer yet. This is an ongoing process, with bits of data coming out sequentially.

Another area of study is to look at patients who have Bence Jones myeloma when the monoclonal light chain protein present in urine. Is it possible to replace the 24-hour urine collection to measure the urine light chains with a blood test to check the level of serum light chains? The urine collection is more precise, so this remains our recommendation at present. There just isn't the same security with the serum test because of the fluctuating numbers. At this time we can say that even though the serum test might reduce the frequency of the urine test, the 24-hour urine collection remains the standard test.

What can you tell us about the new Hevylite™ assay?

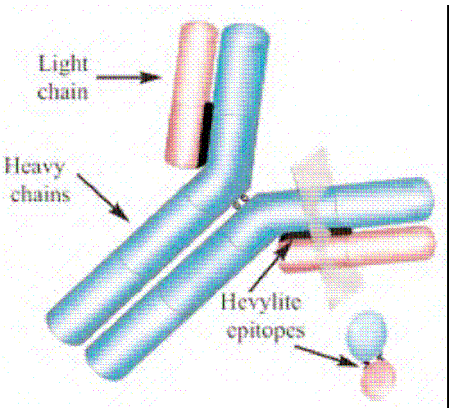
Hevylite™ is a new assay currently being assessed for its usefulness in managing myeloma, which allows us to look directly at the heavy chains of the serum M spike. For example, if you have IgG myeloma, the Hevylite test looks at IgG kappa. Clinically, the Hevylite test is potentially very important because it can actually measure M proteins when they are of low concentration or when they are hidden by other protein bands. For quantifying M proteins, Hevylite promises higher sensitivity than serum protein electrophoresis (SPE or SPEP) and a numerical evaluation not available with immunofixation electrophoresis (IFE). A negative IFE is the definition of CR and, with the Hevylite test, CR would actually become a number that could potentially go to zero.

What is the current availability of the Hevylite test?

In the early part of 2010, the company developing Hevylite (The Binding Site) will be going through the approval process in the US for their IgA kappa and IgA lambda kits, with IgG kits expected to become available three to six months later. This could be very useful for patients with negative or questionable IFE as well as for serial monitoring.

Have there been any Freelite/Hevylite news coming out of the 2009 annual meeting of the American Society of Hematolog y (ASH)?

At ASH, members of the International Myeloma Working Group (IMWG) have reviewed and discussed which clinical studies are most applicable to answer our questions about the use of Freelite and Hevylite in myeloma. It is anticipated that these discussions will lead to fruitful collaboration in the future development and evaluation of these assays in 2010. MT



Target epitopes (in black) for Hevylite antibodies are on the constant regions between the heavy and light chains of immunoglobulin molecules.

Editor's Note: To learn more about Freelite, please see the Understanding Serum Free Light Chain Assays brochure published by the IMF or visit www.thebindingsite.com, and stay tuned for upcoming data from the IMF and the IMWG about the use of Freelite and Hevylite serum assays in myeloma.