

## SERUM FREE LIGHT CHAIN TESTING FOR DIAGNOSIS AND MONITORING

*Myeloma Today* in conversation with Dr. Sundar Jagannath

### Please give us a brief overview of myeloma diagnosis and monitoring.

Multiple myeloma is a cancer of the plasma cells. Cancerous plasma cells start from one single cell and multiply over time into a large population of “monoclonal” cells. Plasma cells make antibodies (proteins also known as immunoglobulins) that can be detected and measured in the blood of approximately 80% of myeloma patients. The monoclonal protein made by the malignant plasma cells gives rise to the M-spike in the serum protein electrophoresis (SPEP) test, which has been used for many years to screen for myeloma, MGUS, and AL amyloidosis. The protein also shows up in the urine as Bence Jones protein, named after the doctor who first published his study of this protein in the urine of a myeloma patient in 1848. For many years, we used simple blood and urine tests to diagnose myeloma, and to monitor treatment and disease progression. These tests were surrogate markers that allowed us to reduce the number of bone marrow biopsies and imaging scans that a patient would have to be subjected to.

### Would you please explain the relationship between cancer cells and antibodies?

The antibody is made up of a big protein, which we call “heavy chain,” and a small protein known as “light chain.” Normal plasma cells make complete antibodies, where one big and one small protein are attached to each other, with each antibody having two sets of these paired proteins. The job of the normal plasma cells is to protect us from infection. But cancer cells are only interested in growing and multiplying, not in making antibodies. Some cancer cells do make big and small proteins in equal quantity – such malignant cells are still good antibody producers – and these proteins show up in the blood as the M-spike, and corresponding IgG or IgA will become elevated.

But other cancer cells become what we would term more “de-differentiated” – they are more immature, reproduce more rapidly, and are less efficient at making antibodies. Sometimes such cells make few big proteins but lots of small proteins, which results in an excess of light chains. In the past, we were not able to measure the light chains in the blood because small proteins can be easily filtered out by the kidneys into the urine as Bence Jones protein. In some patients, the kidneys re-absorb quite a bit of the protein that has been filtered, so the amount of Bence Jones protein that can be measured does not accurately correlate with the amount of light chain protein produced by the cancer cell. So there are groups of patients whose myeloma has historically been difficult to monitor. For monitoring the disease in such patients, there was no alternative to performing frequent bone marrow aspirations and imaging scans.

### How many myeloma patients fall into these categories?

Light chain myeloma occurs in 10%-20% of patients. These patients don't make the heavy protein at all, so no M-spike abnormality can be measured in blood tests. In such cases the IgG or IgA numbers are actually low. But a 24-hour urine collection will reveal lots of light chain protein in the urine so, in the past, this was our best way to measure myeloma in such patients.



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In 2%-3% of myeloma patients, the cancer cells have become so de-differentiated that they have lost all ability to make protein and release it into the blood. This is called “non-secretory” myeloma. In the past, only frequent bone marrow biopsies and imaging scans could effectively help to monitor such patients.

### Has this changed with the availability of the Freelite™ technology?

Well into the year 2000, there was no available serum test to identify the light chain in the blood. We could only measure complete proteins in the blood and the light chain in the urine. Then, thanks to doctors in the UK, there was a major breakthrough in the detection and monitoring of myeloma. They created the antibody that would recognize the light chain. Of course, since all normal proteins have equal numbers of light and heavy chains, it was most important to be able to specifically detect excess light chain protein that was free of the heavy chain. With Freelite Serum

Free Light Chain Assays, we finally had a new technology capable of detecting and measuring free light chain in the blood.

This was a huge breakthrough that made several important things possible. Freelite has enabled us to monitor disease in patients with a monoclonal protein that cannot be measured by conventional electrophoretic methods, so we can now monitor all but a very few myeloma patients. Patients who were previously unable to participate in clinical trials can now have access to the same opportunities as patients with secretory myeloma. Freelite has reduced the need for urine studies, especially the 24-hour urine collection, which can be very impractical or inconvenient for patients. Together with the use of SPEP and immunoelectrophoresis, Freelite has improved the diagnosis of monoclonal gammopathies and the risk assessment for progression of MGUS (monoclonal gammopathy of undetermined significance) to myeloma. For patients with primary or AL amyloidosis, we now have a new way to monitor their disease and measure the efficacy of their treatment. If a patient has both light chain and heavy chain myeloma, Freelite allows us to detect the response to treatment much more quickly than previously possible. Also, in patients who make excess light chain, Freelite is a much more sensitive and precise way to confirm if a patient has achieved complete remission.

The Freelite Serum Free Light Chain Assay is not an experimental test – it is FDA-approved and widely available, so patients can ask for it wherever they are receiving their medical care. This is an important new advancement in technology that has improved the lives of many people living with myeloma and other B-cell dyscrasias. **MT**

Editor's Note: Dr. Jagannath is Chief of the Multiple Myeloma Program and Bone Marrow and Stem Cell Transplantation Program at St. Vincent's Comprehensive Cancer Center (SVCCC) and a professor of medicine at New York Medical College. He has received numerous awards for his work related to the study and treatment of myeloma. Dr. Jagannath is an Editor-in-Chief of *Clinical Lymphoma & Myeloma*. He has been published in numerous medical journals, for which he is also a peer reviewer. Dr. Jagannath is an active member of the American College of Physicians, the American Society of Clinical Oncology, and the American Society of Hematology.

## IMF HOTLINE COORDINATORS ANSWER YOUR QUESTIONS

The IMF Hotline 800-452-CURE (2873) is staffed by Debbie Birns, Paul Hewitt, and Nancy Baxter. The phone lines are open Monday through Friday, 8am to 4pm (Pacific Time). To submit your question online, please email [TheIMF@myeloma.org](mailto:TheIMF@myeloma.org).

### I have been diagnosed with “smoldering myeloma.” Is that an earlier stage than stage I?

There are several names for smoldering myeloma, and they are used interchangeably. Smoldering myeloma, indolent myeloma, asymptomatic myeloma, and Durie Salmon Stage IA myeloma are synonyms for the same condition, as defined in the International Myeloma Working Group’s Myeloma Management Guidelines (The Hematology Journal, 2003). The basic criteria for smoldering or asymptomatic myeloma set forth in the Management Guidelines are: hemoglobin value of  $> 10$  g/dl, serum calcium  $< 10.5$  mg/dl, bone X-ray normal, M-protein rates of  $< 5$  g/dl for IgG or  $< 3$  g/dl for IgA, and  $< 4$  g of urine light chain M-protein on electrophoresis in a 24-hour period. The requirement for smoldering myeloma is that the patient should have no symptoms or organ damage; that is, no Calcium elevation, kidney (Renal) dysfunction, Anemia, or Bone disease — the so-called CRAB criteria.

### Is there anything I can do to prevent smoldering myeloma from progressing to active myeloma?

Because patients with smoldering myeloma are monitored by their doctors without being given treatment, this is an opportune time to concentrate on making life-style adjustments that can have a positive impact on your overall and immune system health: reduce stress, get regular sleep and exercise (nothing risky or high-impact), and eat well (avoid white flour, sugar, and fats, and increase whole grains, fresh fruits and vegetables, and lean protein). Red wine and the skin of red grapes are known to contain resveratrol, an anti-oxidant that is being studied for its anti-myeloma effects. Including these items in your diet, in moderation, may be beneficial as well.

In addition, especially for those who fall into the highest risk group for progression to active myeloma, there are clinical trials studying interventions that may prevent progression. Two that are now enrolling patients are a Phase II trial of celecoxib (Celebrex®), and a Phase III trial of zoledronate (Zometa®) with or without thalidomide (Thalomid®).

### What are the risk factors that my smoldering disease will progress to active myeloma?

In the Fall 2007 issue of *Myeloma Today*, Dr. Robert A. Kyle mentioned his article entitled “Clinical Course and Prognosis of Smoldering (Asymptomatic) Myeloma,” which was published this past June in the *New England Journal of Medicine*.

Dr. Kyle and his colleagues, after long-term study of patients at the Mayo Clinic, used their data to create a three-tier chart that ranks the risks of progression from smoldering to active myeloma. The most predictive criteria, of the many studied, turned out to be the percentage of plasma cells in the bone marrow and the amount of monoclonal protein present in the blood. According to the Mayo data:

- Those at highest risk for progression have 10% or more plasma cells in their bone marrow and 3 grams or more of monoclonal protein per deciliter of blood. There is an 87% chance that within 15 years, they will



Hotline staff: Debbie Birns, Paul Hewitt, and Nancy Baxter

progress to active disease. The median time to progression is 2 years.

- In the middle risk group, patients have 10% or more plasma cells in the bone marrow, but less than 3 grams of monoclonal protein. Their risk of progression to myeloma in a 15-year period is 70%. The median time to progression is 8 years.

- In the lowest risk category, patients have less than 10% plasma cells in the bone marrow and less than 3 grams of monoclonal protein. Their risk of progression to active disease is 39% at 15 years. The median time

to progression is 19 years.

Based on the Mayo study, the overall probability of progression to active disease over a 20-year period is 78%.

In addition, an article recently appeared in the online publication *Blood First Edition* (October 17, 2007) by Dispenzieri, Kyle, et al. of the Mayo Clinic that is entitled “Immunoglobulin Free Light Chain Ratio Is an Independent Risk Factor for Progression of Smoldering (Asymptomatic) Multiple Myeloma.” Dr. Dispenzieri’s research enables clinicians to incorporate the results of the Freelite™ Serum Free Light Chain Assays test. (For more information on this test, please see interview with Dr. Sundar Jagannath in this issue of *Myeloma Today*.) Freelite measures the number of kappa and lambda free light chains and then expresses these numbers as a ratio, into the risk model for progression to active myeloma:

- Patients in the highest risk group whose kappa/lambda free light chain (FLC) ratio is  $< 0.125$  (excess lambda light chains) or  $> 8$  (excess kappa light chains) have a 75% risk of progression to active myeloma at 10 years. Those with a FLC ratio greater than or equal to ( $\geq$ ) 0.125 or less than or equal to ( $\leq$ ) 8 have a 51% risk of progression to active disease at 10 years.

- Patients in the intermediate risk group with a FLC ratio of  $< 0.125$  or  $> 8$  have 57% risk of progression to active disease at 10 years; those with a FLC ratio  $\geq 0.125$  or  $\leq 8$  have a 40% risk of progression at 10 years.

- Patients in the lowest risk group for progression to myeloma who have a FLC ratio of  $< 0.125$  or  $> 8$  have a 25% risk of progression to active myeloma at 10 years; those with a FLC ratio of  $\geq 0.125$  or  $\leq 8$  have a 23% risk of progression at 10 years.

An important caveat to remember in assessing risk is that these models are based on statistics and averages; they do not take into account the individual influences on risk that affect any given patient. They are good general guidelines, but are not entirely predictive of what will happen to you as an individual patient.

### Why isn’t my doctor treating me now, before the myeloma progresses and I have symptoms? I thought that “early detection is your best protection.”

We realize that not treating myeloma before it causes symptoms seems counterintuitive, but randomized studies have failed to demonstrate any added benefit with immediate systemic therapy in patients with asymptomatic (smoldering) myeloma.

CONTINUES ON NEXT PAGE

HOTLINE — continued from previous page

In addition, not all patients with smoldering myeloma progress to active myeloma, and in those who do, progression may not occur for years. Not treating such patients spares them the side effects of treatment and prevents the development of myeloma cells that are resistant to treatment. It also means that by the time treatment might be needed, new and better treatment options are likely to be available.

**How often, and with what tests, should my doctor be following me?**

Depending on where the protein was initially found – urine or blood – the patient should be monitored with that corresponding test – SPEP or UPEP. In addition, baseline Freelite test, CBC, and Chemistry Panel

should be administered, and a set of full skeletal X-rays should be done. Physicians should repeat the lab tests 2 to 3 months after diagnosis to rule out an early active form; if the results prove to be stable, the tests should be repeated every 4 to 6 months. Bone marrow biopsy should be performed at diagnosis, and repeated only if there are signs of progression to active myeloma (i.e. any change in the CRAB criteria or rising lab values on SPEP, UPEP, or Freelite test). **MT**

Editor's Note: For more information, please call the IMF hotline at 800-452-CURE (2873).