Use of a Daratumumab-Specific Immunofixation Assay to Assess Possible Immunotherapy Interference at a Major Cancer Center: Our Experience and Recommendations

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Guest: Dr. Daniel Kirchhoff is recently completed a Clinical Chemistry Fellowship at Memorial Sloan Kettering Cancer Center and is currently an Assistant Director of Clinical Chemistry at the Mount Sinai Hospital in New York, New York.

Randye Kaye: Hello, and welcome to this edition of JALM Talk. This comes from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

Recent advancements in treatments for multiple myeloma have led to the first line use of monoclonal antibody therapies. One such therapy is daratumumab, an IgG kappa monoclonal antibody targeting CD38, a cell surface glycoprotein that is overexpressed on multiple myeloma cells.

While monoclonal antibody therapies have resulted in improvements to the care of multiple myeloma patients, they can also cause interferences on serum protein electrophoresis and immunofixation tests, which are frequently performed in these patients. In order to combat these interferences, a commercial assay called Hydrashift was developed to bind the daratumumab drug in patient's serum samples prior to running serum electrophoresis or immunofixation.

An article appearing in the November 2021 issue of JALM describes the experiences of a major cancer center in using the assay and provides guidelines on its appropriate use.

On today's podcast, we're joined by the article's first author, Dr. Daniel Kirchhoff. Dr. Kirchhoff recently completed a Clinical Chemistry Fellowship at Memorial Sloan Kettering Cancer Center and is currently an Assistant Director of Clinical Chemistry at the Mount Sinai Hospital in New York, New York. Dr. Kirchhoff, welcome!

Let's start with this. Why did your institution decide to investigate the use of the Hydrashift assay? What makes it so useful in interpreting serum protein electrophoresis and immunofixation tests?

Daniel Kirchhoff: Sure. Well, being a large Cancer Center, we process and interpret hundreds of SPEP and immunofixations per week. With the introduction of daratumumab or any monoclonal antibody therapy is leads to the issue of having false positive immunofixation results. That is so patients who have multiple

myeloma or other related conditions, typically have some sort of circulating immunoglobulin clone and we can use this clone (whether it's present or not and how much of it there is) to track treatment and observe a patient's response to treatments. And we do this via whether the clone is still present in the patient serum via immunofixation electrophoresis.

So the issue is that daratumumab itself is a monoclonal immunoglobulin. So, patients who are undergoing daratumumab therapy will always show an IgG kappa clone on their immunofixation. If the patient's clone from their disease and also an IgG kappa, this leads to the issue of how do we tell which IgG kappa clone is due to the patient's therapy, the daratumumab or which is due to their disease.

So the Hydrashift assay is really great because it allows for all the daratumumab in the patient's serum essentially be bound up by those anti-daratumumab antibody. It prevents it from migrating down the gamma region on the patient's immunofixation, where the patient's clone from their disease (if it's present) will typically reside. So basically, it allows us to remove this potential interference on the patient's immunofixation electrophoresis.

Randye Kaye: Okay. Thank you. Now I think you might have already answered this, but I want to make sure in case you want to add something.

Daniel Kirchhoff: Sure.

Randye Kaye: Let's talk about how might be use of Hydrashift help clinicians managing their patient's disease, or did you already answer that?

Daniel Kirchhoff: No, absolutely. So it helps manage the patient's disease and that a lot of patients who have multiple myeloma, they put them in these response criterias as they're undergoing therapy, whether it's very good response and poor response criterias and so on.

And so one of the parameters they use to whether or not the patient is responding to their treatment or their disease is progressing or whatnot is whether or not the patient has a positive clone on their immunofixation. So whether or not if it's a immunofixation positive or immunofixation negative.

So, as I kind of stated that people who are undergoing daratumumab therapy will always have a positive immunofixation electrophoresis. So, if we don't identify this daratumumab interference, either identify or mitigated, patients will always have this false positive immunofixation reaction. This could potentially place them in the wrong

disease response category and could potentially affect their treatments and affect how the clinician will observe this patient's disease progression or being treated.

Randye Kaye: All right, thank you. So, let's talk about the findings of your retrospective study. I want to see if you can summarize the findings, like what value did the use of Hydrashift provide in the cases where it was used?

Daniel Kirchhoff: The goal of the study was to perform this retrospective analysis of every Hydrashift assay we performed at our institution over about two and a half years. We want to not only to say, okay, when do we use a Hydrashift assay, but why do we use this? And from this can we actually come up with the guidelines or recommendations of when this assay is best used.

See from the initial kind of 20 second glance toward the Hydrashift assay, your instinct is we should perform the assay on every single patient undergoing daratumumab therapy, but that's not really a good use of resources: financially, time-wise and so on. But we have found in the results of our study is that the Hydrashift assay is best used in patients that have an IgG kappa clone that co-migrates or travels on the same spot as the gel as daratumumab.

And furthermore, we found that even if the patient had a co-migrating clone, it wasn't necessary to use the Hydrashift assay on every single patients or gel who had this co-migrating clone. It was only useful in patients who had very small M-spikes, or M-spikes that were reduced to a low level of about 0.25 g/dL.

We found that in patients who had M-spikes larger than this, it was highly unlikely that their M-spike or the positivity of the gel would be entirely due to daratumumab, making the Hydrashift assay unnecessary. While patients who had M-spikes below this value of 0.25 g/dL, it was a very good chance that the M-spike immunofixation could be due to daratumumab, making the use of the Hydrashift assay warranted.

Randye Kaye: All right. Thank you. Now according to your article, the Hydrashift assay say isn't necessarily for all multiple myeloma patients undergoing daratumumab therapy. Can you talk about this laboratory stewardship aspect of your study, and why do you feel that that stewardship is important, particularly in this context?

Daniel Kirchhoff: Yeah absolutely. So, we found in the study that if the patient does not have a co-migrating IgG kappa clone, whether it's IgM kappa or IgM lambda whatever, the assay really is not

needed. And furthermore, if a patient had a large M-spike, that is greater than 0.25 g/dL, the assay really was needed.

I mean this is important. It helps reduce unneeded medical care. Now you always hear all these statistics going around that some massive percentage of healthcare is supposedly unnecessary and there's always a thought that this idea of more tests, more results, and so on will lead to better patient care and better patient outcomes.

But here we've shown in our study that just using this Hydrashift assay on every single patient that has daratumumab in their system doesn't really lead to any better patient care, better patient outcomes. It's more, it's not needed, but it's useful in certain circumstances and that's kind of what our study showed.

This kind of raises the idea of lab stewardship comes in. In clinical pathology as laboratories we have this unique opportunity to begin to analyze our tests and analyze our assays and workflows and determine where these assays are most useful. And exercises like this are always useful, but particularly now with his COVID pandemic going on, there's a lot of financial uncertainty built in everyone, but particularly in healthcare. And by performing these sort of exercises, we can conserve financial resources, whether it's financial or others, lab resources. I mean it's always useful exercises.

Randye Kaye: All right. Thank you. And so finally, are there any other solutions that are available or maybe under development to help mitigate these therapeutic monoclonal antibody interferences?

Daniel Kirchhoff: Right. So, unfortunately, the Hydrashift assay is only applicable to patient undergoing daratumumab therapy. So any patient who is undergoing another monoclonal antibody therapy, it unfortunately does not work with that.

But there is currently other similar assays based on the same general idea for other monoclonal antibodies or monoclonal therapeutics such as isatuximab. That concept is basically going to be the same. There's also mass spectrometry techniques that are under development for identifying a monoclonal antibody therapy in multiple myeloma patients as well.

Randye Kaye: All right. Thank you. Thank you so much for your time today.

Daniel Kirchhoff: Great, thank you.

Randye Kaye: That was Dr. Daniel Kirchhoff discussing the JALM Article, "Use of a Daratumumab-Specific Immunofixation Assay to Assess Possible Immunotherapy Interference at a Major

Cancer Center: Our Experience and Recommendations". Thanks for tuning in to this episode of JALM Talk. See you next time and don't forget to submit something for us to talk about.