Transcript Details

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What Are the Pathological Criteria and Markers for Assessing Response to Immune Checkpoint Blockade?

Announcer:
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Dr. Cottrell:
Hello, my name is Tricia Cottrell. I am from the Department of Pathology at Queens University in Kingston, Ontario. And I will be presenting today on the pathologic criteria and markers for assessing response. Why does pathologic response matter? Following neoadjuvant therapy, we have a unique opportunity to assess response in the surgically resected specimen. And it has been found that in the setting of neoadjuvant chemotherapy, patients who have less than or equal to 10% residual viable tumor have a significant survival benefit over those that have greater than 10% residual tumor. And this is what has defined major pathologic response.

More broadly, complete pathologic response and other thresholds of pathologic response have been demonstrated to correlate with patient survival following neoadjuvant therapy. And this is particularly exciting because that makes pathologic response a valuable clinical trial endpoint. You can imagine that rather than waiting years for survival data to accumulate, you can actually have the results of a clinical trial at the time that the last patient has surgery. And so, the possibility of using pathologic response as a clinical trial endpoint could greatly accelerate our ability to get new therapies into the clinic.

This is also critically important because the number of neoadjuvant clinical trials is skyrocketing. So, with the success of immune checkpoint blockade, we now have a unique reason to use these therapies before surgery. It is likely that having that tumor in place at the time of immune activation creates an opportunity for the immune system to be educated about tumor antigens. And then once that specimen is surgically resected, the immune system continues to circulate and maintain a memory of the tumor antigens. This is the reason that there is an explosion in the number of neoadjuvant clinical trials and why pathologic response is such an important topic. In addition, once patients have surgery and we assess the specimen for pathologic response, we can use that information to guide adjuvant therapies. So, based on whether or not the patient seems to have responded to the neoadjuvant therapy, we can make informed decisions about the best course of treatment for the adjuvant setting.

Originally the approach for assessing pathologic response following neoadjuvant chemotherapy was developed based on an approach that really assesses tumor cellularity. So, the approach is basically to take the surface area on a slide and divide it into three categories: viable tumor, necrosis, and stroma. And because there's no specific distinction between intratumoral stoma and treatment effect, this is really ultimately a measurement of tumor cellularity. In addition, there really hasn't been great data in lung cancer to inform the significance of assessing pathologic response in lymph nodes.

So, these are some areas where more recent data has shed significant light on pathologic response assessment. So, using the original first lung cancer specimens treated with anti-PD-1 in the neoadjuvant setting, we were able to systematically identify the features of pathologic response following neoadjuvant immune checkpoint blockade. And we did this using two approaches. First, we compared the

pre-treatment biopsy to the post-treatment resection specimen and we also looked at post-treatment specimens comparing responders to non-responders. And you could see on the right a number of different histologic features that were scored in responders vs non-responders. The data comparing pre- vs post- is not shown. Ultimately, what we identified was a constellation of features that reflected three processes happening in the tumor microenvironment when an effective immune response was mounted. There was significant evidence of immune activation, such as an influx of plasma cells, lymphocytes, and a formation of tertiary lymphoid structures. We also saw evidence of massive tumor cell death, including lipid accumulation in the form of cholesterol clefts or in foamy macrophages. And finally, evidence of tissue repair, including neovascularization and proliferative fibrosis.

We were able to use this constellation of features to identify regression as distinct from other inflammatory and fibrotic processes seen commonly with lung cancers. And using this approach, we developed immune related pathologic response criteria, which really focuses on measuring the treatment response rather than the tumor cellularity. And what you can see on the right is that when pathologists were blinded and asked to score 19 specimens using either the cellularity approach or the regression-based approach, we had much better reproducibility of pathologists scoring using the immune related pathologic response criteria.
This approach was used to score the very important clinical trial, BMS CheckMate 816, which was a study of neoadjuvant Nivolumab plus chemotherapy in resectable lung cancer. This is the phase three clinical trial upon which the clinical approvals are based. And, of course, it showed that the rates of pathologic response, event-free survival, and overall survival improved with the combination IO plus chemo.
We have additional data coming out now that shows that different thresholds of pathologic response are associated with distinct survival outcomes. So, it's important to remember that that 10% residual tumor that defines major pathologic response was validated in the setting of neoadjuvant chemotherapy and we don't know what the most meaningful thresholds of response are in the setting of neoadjuvant immune checkpoint blockade.

We've also recently seen two-year event free survival that associates not only with the percentage of residual viable tumor, which you can see on the left, but also the percentage of regression which you can see on the right. And this data really validates that when we're measuring regression, we're measuring the treatment response, which of course correlates to the patient outcome.

Finally, we've had some interesting preliminary data suggesting that measurements of pathologic response in lymph nodes is going to be an important part of predicting patient outcomes. So, not surprisingly, patients who have involved lymph nodes have the best prognosis when they have a complete response in the primary tumor as well as the lymph node. They have the worst outcome when there's residual tumor in both the primary lung and in the lymph nodes, and then patients with tumor in either the lung or the lymph node have an intermediate prognosis. So, interesting preliminary data, but of course more work needs to be done to validate these findings.

In conclusion, pathologic response correlates with patient survival, can guide adjuvant therapy decisions, and is a valuable clinical trial endpoint. Following neoadjuvant immune checkpoint blockade, histologic features of tumor regression reflect immune cell activation, tumor cell death, and tissue repair. And future studies are needed to define the response thresholds most strongly predicting survival outcomes, after neoadjuvant immune checkpoint blockade, including response assessments in lymph nodes. Thank you for your attention!

Announcer:
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