Let’s Talk About Melanoma Immunotherapies and Immune-Related Adverse Events

A conversation with Dr. Alexandra-Chloé Villani about side effects melanoma patients may experience when receiving immunotherapy.

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Immune-related adverse events (irAEs) are side effects experienced by patients undergoing immunotherapy to treat their melanoma (or other cancer). Some common adverse events include stomach problems that cause inflammation in the large intestine; hormone problems that cause the thyroid gland to be too active, not active enough, or make the body unable to use sugar; and skin problems that cause rashes, flaking, and loss of pigment. More serious side effects, while less common, are also possible and can include damage to the nerves, heart, or lungs.

In November, at the annual Society for Immunotherapy of Cancer (SITC) meeting, we spoke with Dr. Alexandra-Chloé Villani, an MRA-funded investigator at Massachusetts General Hospital, to learn more about immune-related adverse events and the research she leads in this area.

Based at the Krantz Family Center for Cancer Research and the Center for Immunology & Inflammatory Diseases at Mass General Hospital in Boston, Dr. Villani has an interest in immunology and in understanding the drivers of immune-related adverse events. She leads a multi-disciplinary team group that includes physicians, immunologists, genomicists, computational biologists, and scientists working across different divisions of medicine.

The overall goals of her research are to understand what drives the toxicity presented in patients receiving immunotherapy, to identify potential new therapeutic targets, and to identify potential biomarkers to predict who is at risk for experiencing immune-related adverse events or to be able to diagnose patients experiencing adverse events as early as possible when these reactions are most easily treated.

Tell us about your research and how it relates to patients and their care.

Together with my colleague, Dr. Kerry Reynolds, we’ve created the Severe Immunotherapy Complications Service at Massachusetts General Hospital (MGH). Dr. Reynolds serves as Clinical

Director of the inpatient cancer unit, while I oversee the translational (research) program. This multidisciplinary care unit consists of teams of oncologists that work hand-in-hand with different medical specialists to help diagnose and tailor the care of cancer patients that present with suspected immune-related adverse events. As part of their care — and with patient consent — tissue samples are collected for researchers to analyze and try to understand what cells are likely to drive the disease, and to help us understand which of these cells could be targeted for future treatments.

How is your research helping to identify targets to treat these adverse events?

Some initial work that I am pleased to present at SITC includes our research on immune checkpoint inhibitor-associated myocarditis — inflammation of the heart muscle — which is the most fatal immune-related adverse event. It affects only 1% of patients receiving checkpoint immunotherapy drugs but is fatal in 40% of those cases. Through our research, we've identified specific immune cells in the heart that promote inflammation leading to myocarditis. We also identified signals in the blood that may predict if patients are more likely to succumb to myocarditis. Finally, we also identified potential therapeutic targets, some of which are supported with a new clinical trial recently launched at MGH with the goal of mitigating myocarditis while keeping patients on their life saving therapy (NCT05335928).

I'm also presenting results on a study of immunotherapy-induced colitis — severe inflammation of the colon — which is one of the most frequently observed severe toxicities. We have discovered that the mechanisms that drive toxicities in the colon are different from those identified in the heart with myocarditis. Certain immune cell populations in the colon create damage and other non-immune cells contribute to local inflammation. We've identified potential therapeutic targets that could help stop the migration of immune cells to the colon that cause colitis.

Finally, we have ongoing translational research studies on the liver, joints, lungs, nerves, kidney, and endocrine glands. The goal of these studies is to try to find common and distinct biological mechanisms that drive toxicities. If we understand what is common and what is distinct in these organs, then we can rationally think about therapeutic targets and clinical trials.

What should patients who are starting immunotherapy ask their doctor about adverse events?

I want to start by reminding patients that immune checkpoint inhibitors have revolutionized melanoma care and that they should not be afraid of these drugs. They work wonderfully well when they work. It's also equally important to know about the existence of these immune-related adverse events and to always report any side effects to their oncologists and care team. If patients have any of the early symptoms of immune-related adverse events, the earlier we diagnose them, the easier it is to manage. The longer patients wait to inform their doctor, the more complex it can become in terms of the adverse events becoming irreversible. So, don't be afraid of sharing any potential symptoms with oncologists and asking questions about them!

Is there anything else you want our patient community to know about your research?

I’m a PhD scientist and I decided to move my whole research operation to a hospital because I want to make sure that the big data research approaches I use are tailored to problems that patients and clinicians face. It’s been incredibly rewarding to interact with patients and their families and to see how we can all work together to ultimately help their care, and quality of life. It is not sufficient to just cure patients of their tumors; it needs to be done in the context of maintaining the proper quality of life for patients.

As scientists, we are so grateful for the patients — and their families — who take part in research studies. In our research, one of the more challenging aspects of studying the side effects of new immune checkpoint immunotherapies is that animal models treated with the same class of drugs don’t develop most of these side effects. It is critical to be able to partner with patients and their families to be able to find solutions for the prevention and treatment of adverse events and it’s incredibly humbling that patients are so gracious in their contributions to research. I’m so thankful for the opportunity to collaborate with this patient population and for their engagement with us.

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