



## **Melanoma Updates 2021**

# **Potential Toxicities Associated with Immunotherapy in the Treatment Melanoma**

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Dr. Douglas Johnson: Hi, my name's Doug Johnson. I lead the melanoma program at Vanderbilt University Medical Center and Vanderbilt Ingram Cancer Center. And today I'm going to be talking to you a little bit about immunotherapy toxicities and specifically talking about immune checkpoint inhibitors. So, these immune checkpoint inhibitors have really revolutionized the treatment of melanoma. It really has taken melanoma from a disease where we essentially had no good treatment options and very, very little chance of long-term survival, to a disease where now about half of patients have long-term survival, even when they present with a disease that spread metastatic disease. And so, there's been a very dramatic improvement in outcomes for patients. In general, these treatments are also reasonably well tolerated.

So, in general, they're not as intense and toxic as many of our traditional cancer treatments like chemotherapy, but there still can be some side effects. And we call these side effects immune-related adverse events or immune toxicities. And so, the way to think about these is the way these treatments work is they stimulate your immune system to attack the cancer. Well, when they have side effects, they can, it's also related to that same action where the immune system misfires, instead of attacking the tumor or in addition to attacking the tumor, it also attacks our own tissues and cells. And so, this really can present in a variety of different ways. Almost any, any organ system can be affected things like the colon, the skin, the thyroid, the liver almost any organ. You name the organ and it can be affected.

Now the good news is generally the side effects are pretty well managed with medications that calm the immune system back down. So especially steroids can be given and suppress the immune system a bit, sort of modulating the overactive immune system and allow things to go back into balance. And the other good piece of good news is that even when steroids are given to calm the immune system down, it doesn't seem to compromise the immune effect against the tumor. So, these treatments are able to



be given and stop the side effect, but not necessarily compromise the effect of the tumor. The other piece of good news that we've found over time in a number of studies is that patients who have a significant side effect and have to give steroids, and even stop treatment, those patients seem to do at least as well as patients who don't have side effects.

So, there is that general correlation. It's not, it's certainly not true for every patient, but many patients who have side effects and even have to stop early, do just as well as any other patients who doesn't have to stop treatment early. So, there's been not a lot of different research to try to get to the bottom of these side effects. One thing that we still don't know is that why particular patients have side effects? So, it's not clear why, for example, somebody starts treatment and gets a pretty rip-roaring case of colitis, which shows up is diarrhea. Why does that patient get colitis? But the next patient who may have the exact same cancer type and have the exact same treatment, they don't have any problem with colitis. They may get another side effect or may not get any side effects. So, that's still a big area of research and a big unanswered question in the field.

And that's something that our group and many others are trying to address. There has been a lot of progress with these kinds of treatments though. And so, our group and many others have tried to dig into the biology of these different cell types that are responsible. And so, we've made a lot of headway in understanding that these are T-cells, which is a particular kind of immune system cells that really causes the side effects. And so hopefully that will help us design treatments to prevent the side effects or treat them when they do have. We've also recently there's been some, some interesting work to try to understand the chronicity of these side effects. In other words, how long if the side effects do come on, how long do they last and how are they managed? And so, we've actually recently found that that more side effects than we previously thought are longer lasting.

And so, in a group of patients that were with melanoma that were treated with some of the anti PD1 treatments about 40% have more long-term chronic side effects. And so that's something that we need to pay attention to a little bit over time to try and understand which patients get these and potentially how to prevent these and how to improve them over time. We've also done some work recently trying to understand about fatal toxicity. So, the good news is fatal toxicities, and what I mean by that. Well, these are side effects that are so bad that the immune system cannot be brought back under control on patients. A patient can actually die of these side effects. Now the good news is we found that these side effects, these fatal side effects are actually quite rare. They only happen in about, with single drug treatment only about three out of a thousand patients. And then with combination of most aggressive treatments, about one out of 80 patients.



So certainly, higher than we'd like, but less common than some, some treatments like chemotherapy and so forth. And one of the most significant side effects that is that can be some dangerous is inflammation of the heart. And so that's certainly been an area that many of us have been trying to study and try to prevent and treat better. So immune therapy again, is quite revolutionary in many, many different kinds of cancers, including melanoma. I didn't really mention that these treatments can have, can have long lasting responses, not just in melanoma, but many other cancers. And these side effects are ones that that can be problematic and can be bothersome. But again, they compare pretty favorably compared to many other kinds of cancer treatments. And the good news is I think we're learning more every day about these kinds of side effects and hopefully how to manage them better and to prevent them and treat them when they do happen. Thanks for your time.