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How Do Patient Characteristics Impact Adjuvant Therapy in All Stages of Resectable Melanoma?

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Dr. Khushalani:
Hello, my name is Nikhil Khushalani. I'm a Medical Oncologist in the Department of Cutaneous Oncology at the Moffitt Cancer Center, Tampa, Florida. Joining me today is Dr. Mitchell from the University of Pennsylvania. Dr. Mitchell, welcome.

Dr. Mitchell:
Thanks for the introduction. I'm Dr. Tara Mitchell from the University of Pennsylvania Abramson Cancer Center. Happy to discuss melanoma today.

Dr. Khushalani:
Thank you. So what we'd like to try and do today is talk a little bit about stage III melanoma. So patients who have already been resected with node positive disease or in transit metastases, clearly at high risk for recurrence, and then certainly emerging data for stage II resected patients as well for stage IIB and IIC.

So Dr. Mitchell, what patient characteristics do you take into account when making shared decisions with your patients when they are referred to you from your surgical colleagues, having undergone treatment from a surgical standpoint for high-risk stage III disease? Anything particular or pointers for our audience?

Dr. Mitchell:
Yeah, so first of all, we try to see all patients with stage IIB or above melanoma in medical oncology. So our colleagues in surgical oncology as well as head and neck oncology and dermatology are aware to refer these patients with high-risk stage IIB and stage IIC, as well as stage III patients, both for observation because we follow these patients with thorough physical and history every 6 months or more, and also with cross-sectional imaging, but also for the discussion about whether adjuvant therapy is appropriate.

And regarding patient characteristics, I always start with the patient's individual risk based on the AJCC 8 staging criteria. I start by explaining to the patient what their individual risk of recurrence is and the patterns of recurrence. Because remembering these stage IIB and IIC patients, half of the recurrences are going to be local or regional that may be amenable to curative intent surgery, whereas a decent percentage will be metastatic at the time of recurrence. So I talk to them about the patterns and rate of recurrence that's very individualized to their own melanoma. And I also talked to them in stage III, that I'll be testing for BRAF mutation status, so that we'll have the full amount of information available in order to make a decision about adjuvant therapy options, if that's the path we're taking, as well as an observation alone, which is appropriate for many patients based on their risk tolerance.

Dr. Khushalani:
Well, that's great. I think you provide a very broad overview about that. So talk to us a little bit more specifically about BRAF mutational

status in stage III, do you, you know, we now have three approved options for these patients who are BRAF mutant V600E or K, we could consider a year of dabrafenib plus trametinib, you could consider a year of pembrolizumab or a year of nivolumab. How do you make those decisions?

Dr. Mitchell:
That's a great question. And I think one that's a complex conversation with patients that all the medical oncologists have to have. I think that we have, like you said, great data and long follow-up now around 5 years for all three agents. And I think the efficacy data are the same. In all cases, there is a significant - statistically significant and I think clinically meaningful reduction in recurrence. Yet there's no long-term confirmation of survival benefit with any of these agents in the era of current highly effective therapies for stage IV, meaning, you know, I'm very clear with patients that there has not been long-term data suggesting that treating early or adjuvant is superior to observation, and then treatment at the time of stage IV disease given the high rate of disease control in stage IV, and including long-term durable, complete responses and potentially cures in stage IV.

And so taking into consideration that the efficacy is similar with all three agents, I think that it comes down to toxicity and patient preference. So in a patient who has you know, BRAF mutation, I talk to them about the pretty much predictable and reversible side effects that we observe with BRAF and MEK inhibition, and that those can quickly reverse with stopping, holding, or reducing therapy. Whereas with immunotherapy, there's that potential for long-term or permanent toxicity, debilitating, or even life-threatening toxicity, very rare, but a possible, you know, risk that patients have to be comfortable with. And in those with no BRAF mutation, I think when it's the only option, they really have to weigh their personal risk of recurrence with their risk tolerance for that less than 1% chance of severe or life-threatening toxicity or that 15% chance of more severe or lingering toxicity. And so I think that that's how I frame it in terms of toxicity. I don't think that we can really extrapolate data from stage IV to stage III, where we know that immunotherapy first line is preferable whenever possible in stage IV disease, it may not be the case in stage III, we don't really have confirmatory data about the superiority of one therapy over the other for adjuvant therapy in stage III.

Dr. Khushalani:
No, I agree completely. I sort of use some very similar talking points, as you highlighted, you know, what are the patient's preferences? What are the comorbidities do they have? You know if, obviously, they have some underlying autoimmune disorder, we'd shy away from utilizing an immune checkpoint inhibitor, if they have the ability to receive a targeted combination of agents for the BRAF mutant patients. You know, my bias has tended to be for those patients to utilize combination targeted therapy, specifically for the reasons you mentioned that these are - the risk reduction is very similar. You know, at the risk of obviously cross comparison between different studies, these trials that led to the approval of these agents with the exception of CheckMate 238 that compared nivolumab to ipilimumab, for patients with stage IIIB/IIIC resected disease, or stage IV resected disease. The other trials included stage IIIA patient's as well, as long as there was at least a millimeter metastatic deposit within the lymph node that was retrieved.

And I think we're also at that cusp, where some of the older trials mandated the use of, or for the need for a completion lymph node dissection. Whereas pretty much all of the modern generation contemporary trials for adjuvant therapy have stopped at the central lymph node positive without requiring further treatment. So I think that is impacting these patterns of relapse, as you clearly pointed out, and we are seeing more local regional relapses as well. But we cannot lose sight of the fact that, you know, even in stage IIC, about 50% of patients have distant relapses. So really putting all of those into perspective for our patients, you know, the age of the patient, comorbidities, molecular status, you know, what does the patient perceive his or her risk to be? And what would they like to see as time goes by? I think that really makes for a much longer conversation of shared informed decision-making, so that we can, you know, do this together with the patient. I think giving them all of those options becomes really, really important.

One last question before we wrap up this segment, what about resected stage IV disease? Are you preferentially utilizing combination immunotherapy based on the IMMUNED trial? Or are you still sticking with single agent therapy?

Dr. Mitchell:
I'm actually using single agent therapy in those patients, because those patients were included in some of the adjuvant immunotherapy trials for PD-1 blockade in the adjuvant. And so I think it's reasonable that a patient who has a very high risk of recurrence to consider adjuvant therapy with single or dual, given that there are patients with truly oligometastatic biology where there may not be a guarantee of a progression or a rapid progression. I think either option is very reasonable to discuss with patients.

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