Transcript Details

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Applying SDM to Personalize Treatment Discussions on Recurrence Risk Reduction in Patients with Early-Stage Melanoma

Announcer:
Welcome to CME on ReachMD. This activity, titled “Applying SDM to Personalize Treatment Discussions on Recurrence Risk Reduction in Patients with Early-Stage Melanoma” is provided by Prova Education.

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Dr. Mooradian
Well, hello. I'm Dr. Meghan Mooradian from the Massachusetts General Hospital, and I'd like to welcome you to our Patient Clinician Connection on adjuvant immunotherapy in early-stage melanoma. In patients with resected stage IIB to III melanoma, the goal of surgery is cure. However, the risk of recurrence remains a significant concern. Studies have shown that a substantial proportion of patients experience disease reoccurrence within a few years of surgery, highlighting the aggressiveness of this malignancy. In recent years, adjuvant immunotherapy has emerged as a promising approach to mitigate this risk by bolstering the body's immune response against any remaining cancer cells. The ability of immunotherapy to potentially provide durable protection against disease reoccurrence underscores its importance in the post-surgical management of these patients with high risk early-stage disease.

We now have two FDA approved immunotherapies, the PD-1 antibodies pembrolizumab and nivolumab, to consider in the adjuvant setting. Thus, early referral to medical oncologists and coordination of care amongst the different sub-specialties is critical to patient care. Remember, when discussing treatment options, it's important to apply shared decision making to align patient and clinician goals. Today I'll be illustrating my approach to treating resected stage IIB to III melanoma through various clinical vignettes. Let's get started.

Amy is in my office to discuss treatment options for her melanoma. She is 55 years old and had a suspicious mole on the right shoulder. Her PCP referred Amy to a dermatologist and a biopsy of the lesion revealed high-risk stage 2C disease. She underwent complete surgical resection with a wide local excision and a sentinel lymph node biopsy, which showed no evidence of axillary lymph node involvement. Genetic testing revealed no actionable mutations. She was then referred to me by the surgeon to discuss the possibility of using adjuvant immunotherapy to reduce the risk of recurrence. Her ECOG performance status is 0 and she has no medical comorbidities.

Dr. Mooradian:
Morning, Amy. How are you doing today?

Kim:
Overall, I'm doing pretty well. I am worried, though, about my melanoma coming back.

Dr. Mooradian:
No, and that's an incredibly valid concern and the reason we're really meeting today to really think about what are our treatment goals and then, how we really favor moving forward, knowing that we can stick to a more conservative approach, which really focuses on close monitoring, thinking about things like regular exams and scans. But we also have the potential to think about treatments that we can use after surgery to reduce the risk of recurrence.

Kim:
Hmm. Well, I think I'd like to try the medication to reduce the risk of recurrence while maintaining quality of life.

Dr. Mooradian:
No, and of course, I think our goal as oncologists is certainly always to help you live the best life and of course, the longest life. So, as we've talked about previously, you've had a stage IIC melanoma surgically removed. And in stage IIC melanoma, we know that recurrence risk can be as high as 50%, with recurrences happening either locally, meaning in and around where the melanoma first developed, regionally, which are the nearby lymph nodes, and even distant. So, when we think about what we can do moving forward in addition to those things like exams and scans that I talked about, we know now there are two FDA approved medications, pembrolizumab and nivolumab. We'll talk a little bit more about how those drugs work in the time to come, but the main takeaway from the clinical studies is that both of those medications have the ability to reduce the risk of the melanoma coming back. And by and large, the medications are well tolerated.

Personalizing the risk of recurrence for individual patients with stage IIB to III melanoma involves assessing various factors such as tumor characteristics, patient demographics, and genetic profiles. Understanding the patterns of recurrence, which include both locoregional and distant recurrence, aids in tailoring surveillance strategies such as intermittent cross-sectional imaging and regular examinations. Likewise, understanding the ins and outs of treatment options, specifically the pros and cons of adjuvant therapy, is also paramount. Early referral to medical oncologists after the diagnosis of a high-risk stage melanoma, particularly stage IIB and higher, ensures timely evaluation and initiation of appropriate surveillance as well as consideration of adjuvant therapies, thereby maximizing the chances of disease control and long-term survival.

Let's return to our discussion with Amy to ease her mind about disease recurrence and discuss next steps.

Kim:
Can you tell me more about these two drugs? Are they immunotherapy?

Dr. Mooradian:
Yeah, so, both pembrolizumab and nivolumab are medications that bind to PD-1. So this is a protein that lives on the surface of a type of immune cell called a T cell. And this binding stimulates the T cell to really go after any residual melanoma cells that may have been left behind or may have escaped, kind of, after the surgery was performed.

So, it's obviously a lot whenever you're thinking through, well, what would these medications entail in terms of my daily life? So let me walk you through that. Treatment is roughly every 3 to 4 weeks depending on the medication that we use. In the trials that have examined these medications, treatment was up to a year, so I would anticipate, and I always do when we start patients on treatment, that we would have the goal of completing a year of therapy as long as it was well tolerated and as long as it remained in line with your goals.

Both pembrolizumab and nivolumab are anti-PD-1 monoclonal antibodies that are approved by the FDA as adjuvant therapy for resected stage IIB up to stage 4 melanoma.

Currently, both pembrolizumab and nivolumab are included in the NCCN guidelines as adjuvant therapy for stage IIB to III melanoma, regardless of BRAF mutational status, and with a category 1 recommendation. Let me review some of the clinical data from pivotal trials that led to the approval of adjuvant immunotherapy in stage IIB and C melanoma specifically.

KEYNOTE-716 was a multi-centered randomized double-blind placebo-controlled phase 3 trial evaluating the efficacy of 1 year of adjunct pembrolizumab versus placebo. Patients that were eligible for this trial were those who were stage IIB and IIC, fully resected with a negative sentinel lymph node biopsy. In this study, patients were randomized 1 to 1 to adjuvant pembrolizumab 200 mg every 3 weeks up to 1 year, or 17 cycles, versus placebo. The primary endpoint was investigator-assessed recurrence-free survival with key secondary endpoints of investigator-assessed disease metastasis-free survival, overall survival, and safety.

So, this was a positive study with pembrolizumab improving recurrence-free survival compared to placebo in the intent-to-treat population, with a hazard ratio of .62. At the 3-year median follow-up timepoint, 76% of patients were recurrence-free in the pembrolizumab arm, versus 63% in those assigned to placebo.

In the final DMFS in the intent-to-treat population also favored the pembrolizumab arm with a hazard ratio of .59. And looking at that 36-month time cut-off, 84% of patients who received pembrolizumab were distant metastasis-free, versus 74% of those assigned to placebo.

CheckMate 76K also evaluated the role of PD-1 inhibition in high-risk stage IIB and IIC melanoma. However, this featured the drug nivolumab and this was a very similar study design to KEYNOTE-716. This enrolled patients with high-risk stage IIB and C melanoma

who underwent a standard wide local excision with a negative sentinel lymph node biopsy. Patients were randomized 2 to 1 to nivolumab every 4 weeks, versus placebo to up to 1 year.

The primary endpoint of this study was relapse-free survival. Key secondary endpoints included OS, DMFS, and safety.

So, CheckMate 76K was a positive study with nivolumab improving recurrence-free survival versus placebo. The hazard ratio for the study was 0.42 in the intent-to-treat population, and at the 1-year timepoint 89% of patients receiving nivolumab were recurrence-free versus 79% of those who were assigned to placebo.

Nivolumab also improved DMFS with a hazard ratio of 0.47 and at that 1-year timepoint, 92% of patients were without evidence of distant metastasis versus 86% in those who were assigned to placebo.

Kim:
Well, what are the most common side effects of these medications?

Dr. Mooradian:
So that's an excellent question and it's always incredibly important that we think about side effects when we're weighing the pros and cons of any therapy that we'd be using. So, in general, these medications are well tolerated. People can have some mild side effects, fatigue, potentially some irritating things like rash or itch but by and large, a minority of patients have any serious side effect.

Kim:
And what would I do if I experienced any of these side effects?

Dr. Mooradian:
No, and I think that's also, again, an excellent question and that's why we want to make sure you have all of our contact information because the number one thing is that you let us know if there's something that's changing. I just simply want you to call us or tell us if you're feeling any different. And if that were the case, we would potentially either work with you over the phone or have you come in to get checked out to sort out, are you having a side effect, and if so, how best can we manage it. We know there are supportive medications that we can use, things like topical steroids if people develop rash, use of over-the-counter medications like ibuprofen if people are having a little bit of joint ache.

The toxicity profiles of pembrolizumab and nivolumab in the pivotal trials were very similar and consistent with previous findings in other settings. Regarding immune-related adverse events, thyroid events were the most common side effects seen. Most adverse events were low-grade and manageable.

The safety data from KEYNOTE-716 showcased a generally mild toxicity profile of pembrolizumab. So, similar to other studies, we can see that overall, the drug is generally well-tolerated. The majority of AEs experienced by patients are grade 1 and grade 2, with approximately 10% of patients experiencing a grade 3 immune-related adverse event.

The individual toxicities experienced by patients most commonly occurred in endocrine organs, particularly the thyroid, where we saw rates of hypothyroidism or hyperthyroidism exceeding 10 to 17%. Other endocrinopathies were seen – hypophysitis in approximately 2% of patients; in other areas of end-organ dysfunction, in only 1 to 2% of patients enrolled in the study. This included side effects like colitis, hepatitis, and nephritis.

The side effect profile of nivolumab in CheckMate 76K mirrors that of pembrolizumab in KEYNOTE-716, with the majority of side effects seen being grade 1, grade 2, and manageable, with approximately 10% of patients experiencing a grade 3 irAE.

Five percent of patients had a treatment-related toxicity that led to discontinuation. And when we're thinking about the exact toxicities experienced by patients, very similar, we're seeing that endocrinopathies seem to be the dominant toxicity with hypo and hyperthyroidism accounting for the majority of toxicities in this space.

Dr. Mooradian:
So, Amy, how are you feeling about the information we've gone over so far?

Kim:
It is a lot to take in but thank you so much for explaining the medications and what to expect as far as side effects.

Dr. Mooradian:
No, you're very welcome. And I think if we feel collectively that the risk benefit ratio is acceptable to think about starting the adjuvant immunotherapy, I would suggest we aim to start treatment in the coming weeks. I know from reviewing your medical history, we don't have any contraindications to using these medications, so I really feel comfortable starting treatment whenever is convenient for you in

the coming weeks. And as we discussed, I'll certainly see you before each infusion, so we can talk about any concerns that you may have, and then ensure that before we go forward with the infusion, everything is safe. And we'll really just take it dose by dose.

Kim:
Thank you, Dr. Mooradian, for discussing these treatment options with me. I do feel comfortable with the possible risks as well as a year of therapy. The potential to reduce the risk of disease recurrence is important to me, and I would like to move forward with immunotherapy.

Dr. Mooradian:
Well, it was my pleasure reviewing all this with you today and I think we have a good plan moving forward. And as of now, me and my team will just work to help transition through this next phase in terms of treatment.

Individualized conversation with patients takes time and energy, but it's certainly worthwhile. Family engagement and involvement are crucial to identify which patients feel comfortable with the risk of toxicity and have the goal of reducing the risk of recurrence. We need to reassure patients and their caregivers that we will take good care of them and be vigilant about follow-up.

I think the case presented in these vignettes can be adapted to address the many scenarios we face daily in our medical practices when discussing diagnosis of and treatment for resected early-stage melanoma. When prescribing adjuvant immunotherapy for these patients, it's important to apply shared decision-making with consideration of patient preferences, potential advantages of treatments, and challenges of treatment adherence to maximize efficacy.

Thank you for joining me for the Patient Clinician Connection vignettes on shared decision-making in the management of patients with early-stage melanoma. Goodbye.

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