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Sequencing Systemic and Local Therapy in HER2-Overexpressing Metastatic NSCLC

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Dr. Levy:
This is CE on ReachMD, and I'm Dr. Benjamin Levy.

Dr. Khandekar:
I'm Dr. Melin Khandekar.

Dr. Levy:
Great to have you, Melin. So let's just start with a case. A patient who's a 64-year-old male who initially presents with cough and shortness of breath, and unfortunately, in the workup of this, is found to have advanced adenocarcinoma of the lung. The patient is a former smoker.

The biopsy is done and it doesn't reveal any genomic alterations, but importantly, it does reveal HER2 overexpression 3+. This patient, without an actionable alteration, is initially treated with chemotherapy and immunotherapy. The PD-L1, let's say, is 10%. At the time of diagnosis, prior to chemoimmunotherapy, the patient did have some asymptomatic brain mets. So patient gets chemoimmunotherapy but unfortunately does develop disease progression below the neck and the chest, and also now these brain mets are more active and there's some CNS progression as well.

So kind of an overview here, general approaches. Melin, how would you take a patient like this? What would be your approach to a patient with CNS progression here on initial chemotherapy and immunotherapy?

Dr. Khandekar:
Thanks so much, Ben. I think this is unfortunately a common situation that we see in lung cancer, and it really depends on a lot of different factors. I would say the first question is, is the patient becoming symptomatic from these lesions? Because that really colors the discussion of do we continue with a systemic therapy approach or a local therapy approach. It's been wonderful to see from a local perspective that there are really good systemic therapy options, and I think often in people with asymptomatic small brain metastases, starting with chemoimmunotherapy as a first line is great.

If the patient is starting to be symptomatic, we start to think about local therapy, whether that's radiation, in some cases surgery depending on the degree of mass effect, the size of the tumor, the number of locations.

And then the other important factor is what is the progression of his extracranial disease. So if there's rapid extracranial progression, we have to prioritize that as well. And it's really a discussion between medical oncology and local therapists, neurosurgeons or radiation oncologists, about how do we interdigitate these and what is the likelihood of response that we might see to systemic therapy.

Dr. Levy:
Yeah, that's great. Interdigitation and collaboration, I think, are going to be really important when we start talking about how to manage these patients with CNS progression.

Dr. Khandekar:
Yeah, I think that that's really one of the main messages that hopefully people can take away, is that the management of brain metastases is really a team effort. And that includes medical oncology, it includes radiation, neurosurgery, neuro-oncology. We often use input from our neuropsychology team about the potential impacts of our local treatments on neurologic function and quality of life, because ultimately those all can be affected by treating the brain. And that comes down to location of metastasis, size, the amount of edema, the need for steroids, and these are decisions best made as a group because there's interactions amongst all of the choices that we have.

Dr. Levy:
Yeah, and I think we need to remember also this patient had HER2 3+ overexpression, and the question is how does trastuzumab deruxtecan come into play here? And as you mentioned, this is a discussion between medical oncology and radiation oncology. There's good data now with trastuzumab deruxtecan post chemo-IO in patients that are HER2 3+. And this is a consideration here.

We've got data from the DESTINY-Lung01 study as well as data from DESTINY-Lung03 as well as the DESTINY-PanTumor study, showing bottom line here is that patients who have HER2-overexpressing tumors that are 3+, response rates north of 50% below the neck systemically, and we are seeing responses in the brain as well in these patients. So I think it's really important that this [trastuzumab deruxtecan] is a drug that is active and also has CNS penetration. We need more data on this, but this enters into the discussion about do we do radiation? Do we do trastuzumab deruxtecan? How do we put this all together?

Melin, if this patient were to have prior stereotactic radiosurgery, or let's say the patient at the time of diagnosis had several brain mets, the decision was to give SRS to these brain mets first, and then now at the time post chemo-IO had CNS progression, how does this change your calculus?

Dr. Khandekar:
Yeah, it's something we certainly would think about, and it really depends on the nature of the CNS progression. So if there's local progression and we feel convinced—and this is often a question—is what we're seeing locally treatment effect or radionecrosis? Is it true disease progression? Are there multiple new lesions? If it's already had radiosurgery, I tend to think that more radiosurgery doesn't make sense, and we have to think about alternative approaches versus new lesions.

Dr. Levy:
How often are you using whole-brain radiation therapy versus really trying hard to deploy other strategies to avoid that? How common is this happening in your practice?

Dr. Khandekar:
It's a great question, and I will say that this has been a moving needle for the past decade or more.

Recently there was a trial published in *JAMA* by Dr. Ayal Aizer at the Dana-Farber Cancer Institute and Brigham and Women's Hospital that looked at patients with up to 20 brain metastases, randomizing them to hippocampal-avoidant whole-brain radiation versus radiosurgery, showing that there was no decrease in survival with choosing a radiosurgery approach and avoiding whole-brain and a significant improvement in a variety of measures of quality of life.

I will say that has justified moving the needle away from whole brain as much as possible. I think there still are patients where we do consider whole brain, where there's many metastases. I've treated people with 40, 50, 60, 70 brain metastases.

Dr. Levy:
Yeah, we share in sort of your journey. I think our radiation oncologists certainly share that avoidance if possible. It's not that you can avoid it all the time, but really trying to deploy other strategies to avoid this.

This is becoming front and center for medical oncology as well, because some of the mutations that we are unearthing in lung cancer, we know if we deliver targeted therapies, the CNS penetration is so exquisite that we can really try to stay away from this.

We could mix up this case a little bit. There's a lot of questions for medical oncology here. If this patient were HER2 mutated, what would we do? And certainly that changes things a lot for us. For a patient who has CNS progression on potentially chemo-IO or even trastuzumab deruxtecan, this would be an opportunity for some of these new tyrosine kinase inhibitors that have been approved in the space. And certainly the CNS response rates are 40%, 50%, 60%, so that would potentially circumvent the need for radiation approaches. So clearly HER2 mutated is a little bit different than HER2 overexpressed.

And then some questions if this patient were HER2 amplified, just sort of a nugget for the medical oncologist there, I'm not sure we really know how to manage lung cancer that's HER2 amplified. We certainly know with HER2 overexpression 3+ that trastuzumab deruxtecan is an option. It has potential CNS penetration. We know with HER2-mutated lung cancer, that trastuzumab deruxtecan is certainly an option, but there's these other TKIs that now play in that can offer meaningful improvement as well as CNS penetration.

So very exciting time. Melin, any parting shots on this case?

Dr. Khandekar:
I think that you hit the nail on the head when you say that we're now in a newer era where we can use systemic therapy to treat microscopic and small disease in the brain very effectively, and that's really enabled us to mitigate some of the toxicities that we saw with large fields of radiation. So it again highlights the collaborative approach, I think, and that's where having a multidisciplinary discussion about these patients to try to optimize for that particular patient both the disease control but also quality of life outcomes is so important.

Dr. Levy:
Great summary there. With that, our time is up. We hope you found this case discussion helpful, and thanks so much for listening.

Announcer:
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