Transcript Details

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Unlocking the Potential of HER2-Targeted Therapy: Breakthroughs in NSCLC Therapeutic Approaches

Announcer:
Welcome to CME on ReachMD. This activity, titled "Unlocking the Potential of HER2-Targeted Therapy: Breakthroughs in NSCLC Therapeutic Approaches" is provided by Prova Education.

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Dr. Yu:
Hello. I'm Dr. Helena Yu from the Memorial Sloan Kettering Cancer Center and I'd like to welcome you to our Patient Clinician Connection on HER2 targeted therapy in non-small cell lung cancer, or NSCLC. Therapeutics targeting actionable oncogenic drivers in non-small cell lung cancer have shifted the treatment landscape and have dramatically improved outcomes for patients. Use of broad molecular profiling ensures that patients receive the appropriate therapy.

HER2 mutations are observed in 2 to 4% of non-small cell lung cancer and are more common in females and never-smokers. And we now have an FDA approved targeted therapy to consider for non-small cell lung cancer patients harboring these mutations. Remember, when discussing treatment options, it's important to align patient and clinician goals.

Today I'll be illustrating my approach to treating HER2 mutations in non-small cell lung cancer through clinical vignettes. Let's get started.

Case discussion: Susan is in my office to discuss treatment options for non-small cell lung cancer. She is 59 years old, a never-smoker, and has well-controlled hypertension. She received platinum-based chemotherapy and her disease progressed after 6 cycles. Her ECOG performance status is 1.

Fifty-nine years old. Past medical history: well-controlled hypertension. Physical exam: no lymph node enlargement. Lungs are clear. Recent complaint of increasing shortness of breath. Her next generation sequencing molecular testing showed a HER2 exon-20 mutation. ALK EGFR ROS1 BRAF RET and MET were all negative, and her PDL-1 percent positivity was less than 1% or zero.

Dr. Yu:
Hi Susan, how are you today?

Susan:
Well, overall, I'm feeling pretty good, but I have some shortness of breath that's preventing me from playing pickleball.

Dr. Yu:
Oh, that's too bad. I know how much you like playing pickleball. I had mentioned previously that your cancer has something called a HER2 mutation and since the cancer has grown on chemotherapy, we need a new treatment. We have this recently approved option that is really effective at treating your specific type of lung cancer. I'm hoping that once we get you on treatment, you're going to go back to doing some of those things you enjoy.

Susan:
Well, this sounds overwhelming. I mean, what does this mean?

Mutations in the gene encoding human epidermal growth factor receptor 2, HER2 for short, also called erbB-2, drive approximately 2 to 4% of non-small cell lung cancers and are associated with the female sex, never-smoking history, and a poor prognosis, as well as with a slightly younger age and a higher incidence of brain metastases than non-small cell lung cancer without HER2 mutations, or with other mutations.

Next generation sequencing, or NGS testing, enables us to identify specific alterations such as HER2 mutations, and guides our use of targeted therapies to more effectively treat our patients. We now have an FDA approved targeted therapy to consider for non-small cell lung cancer patients harboring these mutations. HER2 mutations are distinct from the increased HER2 expression that is seen in breast cancer and some lung cancers.

Let's return to our discussion with Susan to ease her mind about this mutation and discuss next steps.

Dr. Yu:
I know it seems like a lot, but we now have this new FDA approved drug called trastuzumab deruxtecan, T-DXd for short. It has shown some promising results in non-small cell lung cancer with the HER2 mutation.

Susan:
Can you tell me more about T-DXd? Is it chemotherapy?

Dr. Yu:
It's actually a hybrid between chemotherapy and targeted therapy. It's a medication that targets HER2, which is a protein that's on the cancer cell surface. Because of the HER2 mutation in your cancer, we're able to use this treatment.

I know that starting a new treatment can seem overwhelming, so let's walk through how the treatment would go. You'd come into my office, and you'd receive this treatment through an IV every 3 weeks. After a few cycles, we would repeat scans and make sure that things are working.

Trastuzumab deruxtecan, T-DXd, is an antibody drug conjugate consisting of a humanized monoclonal antibody that targets HER2 linked to a topoisomerase 1 inhibitor chemotherapy payload through a tetrapeptide-based cleavable linker. Its formulation incorporates a potent cytotoxic payload at a high drug-to-antibody ratio, or DAR, allowing it to remain stable in plasma until internalized by the cancer cell. It is then cleaved by peptides, releasing the highly potent chemotherapy payload, which induces DNA damage and apoptosis within the lung cancer cell.

Dr. Yu:
Within the NCCN Guidelines for management of HER2 mutant lung cancer, initial therapy is actually carboplatin-based systemic chemotherapy. After progression or intolerance of chemotherapy, second-line therapy is trastuzumab deruxtecan as discussed. If not doing trastuzumab deruxtecan, the standard-of-care would be second-line chemotherapy.

T-DXd is approved for adult patients with unresectable or metastatic non-small cell lung cancer whose tumors have activating HER2 erbB-2 mutations as detected by an FDA-approved test and who have received a prior systemic therapy for the treatment of non-small cell lung cancer.

Let me review some of the clinical trial data for T-DXd. The first study was DESTINY-Lung01 which treated 91 patients with HER2-positive non-small cell lung cancer. It assessed the dose of T-DXd of 6.4 mg/kg where all patients received this dose. The overall response rate was 55% and this was centrally confirmed by independent radiologic review. The median duration of follow-up for patients was 13.1 months. The median duration of response was 9.3 months, the median progression-free survival was 8.2 months, and the median overall survival was 17.8 months.

So, DESTINY-Lung02 was a randomized Phase 2 study that assessed two doses of T-DXd, 5.4 mg/kg and 6.4 mg/kg. Patients with HER2 mutant non-small cell lung cancer that progressed after first-line chemotherapy were eligible. The primary endpoint of this study was confirmed overall response rate by BICR, independent central review.

Dr. Yu:
When assessing the efficacy data from DESTINY-Lung02, the efficacy, the overall response rate, between 5.4 and 6.4 mg/kg were quite similar. However, the toxicity of the two doses were different. The toxicity of the 5.4 mg/kg dose was significantly less. Based on combining efficacy and toxicity, the recommended dose moving forward, and FDA-approved, is 5.4 mgs per kg every 3 weeks.

Susan:

What are some of the most common side effects with this medication?

Dr. Yu:
So, similar to the chemotherapy, you can get fatigue, hair loss, and some GI symptoms like nausea, vomiting, and diarrhea. Rarely you can get something called pneumonitis, which is inflammation of the lung that can lead to symptoms like cough, or shortness of breath.

Susan:
Hmm. What do I do if I experience any of these side effects?

Dr. Yu:
If you have any of these new side effects you should call my office, and depending on the severity, we have different ways to manage it. We can reduce the dose of the medication or delay the medication for a few days, and we also have supportive care medications that can help with symptoms that you might have.

The safety of T-DXd at 5.4 mg/kg every three weeks was shown in the DESTINY-Lung02 clinical trial in pretreated HER2 mutant non-small cell lung cancer.

With ADCs like trastuzumab deruxtecan, you can see different cytopenia including neutropenia and thrombocytopenia. Also, chemotherapy related side effects like fatigue and alopecia can be seen, as well as nausea, vomiting and diarrhea.

Most adverse events on study were low grade and manageable. Rarely, significant toxicity such as pneumonitis or cardiotoxicity can occur. There needs to be a high level of suspicion for these rare, but serious toxicities as they are better addressed early on before the issues progress.

Dr. Yu:
Susan, how are you feeling about all of this new information?

Susan:
Well, it's a lot to think about, but thank you for explaining the medication for me, and what to expect as far as side effects.

Dr. Yu:
Absolutely. After starting this new medication I'd like to set up a quick follow-up visit so we can discuss any side effects and make sure that you tolerate the drug. Please call me if you have any new side effects or issues. And I plan on seeing you every 3 weeks for these drug infusions, and happy to see you between visits if any symptoms arise.

Susan:
Well, thank you Dr. Yu, for discussing this treatment option with me. I'm ready to begin the next phase of my treatment.

Dr. Yu:
Great.

I think the case presented in this vignette can be adapted to address the many scenarios we face daily in our medical practices when discussing the diagnosis of, and treatment for HER2 mutations in non-small cell lung cancer. When prescribing TX – T-DXd for these patients, it is important to apply shared decision-making with consideration of patient preference and potential advantages, as well as challenges in treatment adherence to maximize efficacy.

Dr. Yu:
Thank you for joining me for these Patient/Clinician Connection vignettes on shared decision-making in the management of non-small cell lung cancer with HER2 mutations. Good-bye.

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