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Diving into the Efficacy & Tolerability of mBC Treatment

Dr. Chalasani:
Patients with metastatic breast cancer are on treatments for a prolonged duration, and it is critical to always balance their quality of life with efficacy or treatment outcomes. As such, capecitabine has always been a frequently used medication in the treatment of metastatic breast cancer. It is an oral chemotherapy drug with minimal hair loss and is preferred by physicians and patients. However, the current approved dosing has cumulative toxicity, which present as a frequent barrier for continuation of therapy in clinic, so in a recent study, investigators conducted a randomized trial to compare the efficacy and tolerability of fixed-dose capecitabine, which will be the basis of today's discussion.

Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and joining me today to talk about the X-7/7 trial is Dr. Colleen Bohnenkamp, who is an Oncology Clinical Pharmacist who specializes in women's cancers at the University of Kansas Cancer Center.

Dr. Bohnenkamp, thank you for being here today.

Dr. Bohnenkamp:
Thank you, Dr. Chalasani. I'm so excited to be here with you this morning.

Dr. Chalasani:
To set the stage for our conversation, Dr. Bohnenkamp, can you just briefly walk us through what capecitabine, the current dosing, and how we use it in clinic?

Dr. Bohnenkamp:
Yes, definitely. So capecitabine, as you mentioned, is an oral chemotherapy medication. Specifically, it's a prodrug of fluorouracil or IV 5-FU, which we use in a variety of different disease states; so it's used in breast cancers; it's used in a variety of different GI cancers; and it can be used as a radiation sensitizer, as well in certain other disease states. It's important to understand that it's a prodrug of 5-FU because if you've given 5-FU infusionally in other disease states, it's often given with IV leucovorin, which is a folic acid derivative, and it's important to understand this because we see a lot of differences in tolerability of capecitabine and 5-FU based on the geographic area in which a patient lives. For instance, in the United States, patients tend to have much worse tolerability of capecitabine because we have a higher folic acid content in our diet as compared to those in Asian countries for instance. So this is why it's important to understand this basis because the FDA-approved dose is 1,250 milligrams per meter squared twice a day for two weeks on and one week off. However, many providers will attest that this dosing is very difficult to have patients maintain on due to adverse effects.

Dr. Chalasani:
That is correct. So what are the adverse effects that we frequently see with the standard dose of therapy?

Dr. Bohnenkamp:

Yeah. So the most common side effects that can really be life-altering in patients is what's called hand-foot syndrome, also called PPE, palmar-plantar erythrodysesthesia, and this is peeling, redness, and tenderness that often occurs on the hands and the feet. There can be blistering, and this can result in a lot of debility in patients. Also, we see a lot of diarrhea and mucositis, and really, stomatitis can occur. We can see some neutropenia and hematologic toxicities, but in contrast to IV chemotherapy, this is less of a dose-limiting side effect and less of a cumulative side effect.

The benefits, which I always like to highlight to patients as well—and as you mentioned in the introduction—is capecitabine in contrast to IV chemotherapy. People don't lose their hair; it has low emetogenicity, so patients aren't nauseous and vomiting with these medications, and there's no peripheral neuropathy. And so some of those cumulative toxicities that we often see with IV chemotherapy are spared with this oral option, so it makes it a really desirable treatment option for patients because they can be on it for a long period of time assuming they're not having some of these side effects, such as hand-foot syndrome and significant amounts of diarrhea or mucositis.

Dr. Chalasani:
So now, let's turn our attention to the exciting X-7/7 trial. Can you take us through the design of the study?

Dr. Bohnenkamp:
Yes, definitely. So this was a randomized trial that enrolled female patients with pathologically confirmed metastatic breast cancer. They could have any previous lines of chemo or endocrine therapies, and they could have any breast cancer subtype, so they could be triple-negative or HER2-positive. Our HER2-positive cohort did receive capecitabine in combination with trastuzumab. And then we also had hormone receptor-positive patients as well. One thing I do want to highlight with this is given that capecitabine is adjusted based on renal function, we did only include patients that had a creatinine clearance over 50. We then stratified patients based on their line of chemotherapy, so if this was their first line of cytotoxic chemotherapy or second or subsequent line, those that had measurable or nonmeasurable disease, and then their estrogen receptor status. They were then randomized to one of two arms. So the experimental arm was the fixed-dose, seven and seven arm, and so I want to really underscore that this was evaluating a fixed dose of capecitabine and an alternative schedule of capecitabine. So patients received a fixed dose of capecitabine, which was 1,500 milligrams twice a day—they received this for seven days on followed by a seven-day break, and that was repeated—versus the control arm, which was the standard dose of capecitabine, so 1,250 milligrams per meter squared twice a day for 14 days on and seven days off. And then our primary endpoint of the study was three-month progression-free survival. Secondary endpoints included progression-free survival, overall survival, objective response rate, and toxicity.

Dr. Chalasani:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and I'm speaking to Dr. Colleen Bohnenkamp about the X-7/7 trial, which is looking at an alternative dosing and schedule for capecitabine for patients with metastatic breast cancer.

So, Dr. Bohnenkamp, what were the results of the study?

Dr. Bohnenkamp:
Yes. So our primary endpoint of three-month progression-free survival was 76 percent in both the fixed-dose seven and seven arm and in the standard-dose 14 and seven arm. We also did landmark analysis of progression-free survival, so we also saw no differences in 12-month, 24-month, or 36-month progression-free survival. When we look at our secondary outcomes of objective response rate, we saw an 8.9 percent response rate in the fixed-dose arm compared to 19.6 percent in the standard-dose arm, though this was not statistically significant. And then we also looked at overall survival. Again, looking at three-month, 12-month, 24- and 48-month overall survival, we saw no significant differences in overall survival at any of those cutpoint times, and median overall survival was not different between the two groups either.

What's interesting about our study statistically is if you look at our Kaplan-Meier curves, which I know you can't see on a podcast, you'll see the Kaplan-Meier curves cross, and so what that means is that there's nonproportionality of the data, meaning that you can't evaluate a median PFS or a median OS because it doesn't give a true picture of what's going on as those Kaplan-Meier curves are crossing. So we actually looked at restricted mean survival time, which evaluates an area under their survival curve between a specific

cut point of time. So as far as progression-free survival, we looked at a 36-month restricted mean survival time, and we saw that the restricted mean survival time was 13.9 months in the fixed-dose seven and seven arm compared to 14.6 months in the standard-dose 14 and seven arm, and similarly, looking at overall survival for restricted mean survival time, it was 24.5 months in the fixed-dose arm compared to 20.9 months in the standard-dose arm, so again no significant differences in PFS or OS.

Dr. Chalasani:
That's great. So how significant are the findings? Do you see these impacting the prescribing practices in clinic?

Dr. Bohnenkamp:
So as far as toxicity, we saw significantly lower rates of grade two through four diarrhea, hand-foot syndrome, and oral mucositis in the fixed-dose arm compared to the standard-dose arm.

So grade three or four toxicity occurred in 27 percent of patients in the standard-dose arm compared to only 11 percent in the fixed-dose arm. We saw significantly higher rates of treatment discontinuation and dose modifications that were required among patients in the standard-dose arm as compared to the fixed-dose arm, which is what we were expecting to see is much better tolerability of this fixed-dose seven and seven schedule compared to the standard-dose 14 and seven schedule.

Dr. Chalasani:
Absolutely. I think I was really excited to see the difference in the toxicity between both, and I have to say that is something we frequently do in clinic, eventually, as the toxicities cumulatively accumulate for the patient, and we frequently end up coming to this schedule, so it's kind of nice to see in the trial setting where the data shows that you could do that from the beginning, which has less toxicity for the patients and still maintaining efficacy. And that is important for our patients with metastatic breast cancer who do have a prolonged life, and maintenance of quality of life is such an important thing.

So before we close, Dr. Bohnenkamp, do you have any final thoughts or takeaways you would like to share with our audience?

Dr. Bohnenkamp:
I agree exactly with what you said as I think a lot of people were doing some variation of either seven and seven dosing or fixed dosing, and I think that this gives us a lot more reassurance in educating patients that we're not compromising the efficacy of these medications, and we're still giving them a great treatment option that they can maintain for a longer period of time.

The last thing I wanted to say—and I really loved this quote that the discussant had mentioned during the ASCO presentation—was, "Drugs don't work in people who don't take them." And I think that this is a very important thing that we always need to keep in mind as our drugs are only good in those patients that are taking them, and if we are unable to maintain patients on a medication that's effective, then we're not really doing our best job. And so finding ways to keep people on effective medications is truly important, especially, when we are in a palliative setting where we want to maintain a good quality of life in our patients.

Dr. Chalasani:
Absolutely. This study was very clinically meaningful in how it helps us take care of our patients. So I want to thank my guest, Dr. Colleen Bohnenkamp, for discussing the X-7/7 trial with me today.

Dr. Bohnenkamp, it was a pleasure speaking with you.

Dr. Bohnenkamp:
You as well, Dr. Chalasani.

Dr. Chalasani:
I'm Dr. Pavani Chalasani. To access this and other episodes in our series, visit ReachMD.com/ProjectOncology, where you can Be Part of the Knowledge. Thanks for listening.