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Conversations Around Chemotherapy: Do All of Your Patients Need It?

Dr. Chalasani:
Chemotherapy has been shown to improve outcomes in patients with hormone receptor-positive, HER2-negative breast cancer. But, do all patients really need it? Not only that, they come with a bag of several side effects. Emerging trial data may help us better understand who among our patients with hormone receptor-positive, HER2-negative, node-positive breast cancer would benefit from chemotherapy and who could safely avoid it.

Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani. And joining me today to share key findings from the RxPONDER trial is the lead author, Dr. Kevin Kalinsky, Director of Glenn Family Breast Center at the Winship Cancer Institute at Emory University.

Dr. Kalinsky, thanks for joining me today.

Dr. Kalinsky:
Dr. Chalasani, thanks for including me.

Dr. Chalasani:
To start us off, can you give us a brief overview of the RxPONDER study and the key objectives the study focused on?

Dr. Kalinsky:
RxPONDER was a study of 5,000 patients where—5,000 patients being randomized if they had hormone receptor-positive, HER2-negative breast cancer with 1 to 3 nodes involved and the recurrence score was anywhere between 0 to 25. If the recurrence score was greater than 25, patients were not followed as part of the study but were recommended to receive chemotherapy followed by endocrine therapy. And for the 5,000 or so patients who met the criteria, the eligibility criteria, it was randomized in a 1:1 fashion to chemotherapy followed by endocrine therapy versus endocrine therapy alone. And the objective of the study was to determine the potential benefit in this population of chemotherapy or not and to look at whether chemotherapy was prognostic and/or predictive in this particular population.

Dr. Chalasani:
Can you just share some highlights of the key findings?

Dr. Kalinsky:
So the primary endpoint of the study was looking at invasive disease-free survival, and we reported the initial data at San Antonio at the 2020 conference and then published a follow-up of this in the New England Journal of Medicine in December where we saw a significant difference between postmenopausal and premenopausal women, and this was a preplanned analysis. And for the postmenopausal women, you know, we saw that for invasive disease-free survival as well as additional endpoints like distant relapse-free survival, and we also had a presentation at San Antonio in 2021 where we looked at distant relapse-free interval, and across the board with all of those endpoints we saw for postmenopausal women that there was not an improvement of giving chemotherapy in these patients when looking at those particular endpoints. And if you look at five-year outcomes, there was no difference. We couldn't find a subgroup where there was a benefit. This was different than the premenopausal women where we saw across all of those endpoints that there was a statistically significant benefit across recurrence score 0 to 25 for the patients who were randomized to receive chemotherapy versus those that were not.

Dr. Chalasani:
Great. So given the results of this trial, where do you see how clinicians use this assay in routine practice?

Dr. Kalinsky:
We've seen from the prospective study TAILORx that there was—for patients with node-negative breast cancer that was hormone receptor-positive, HER2-negative disease, that there was a benefit in terms of the clinical utility of the Oncotype score. What we didn't know were for patients with node-positive disease.

I do think that this study helped establish the clinical utility of this assay. You know, for our patients with postmenopausal—who are postmenopausal, clearly there was not a population of patients who had one to three positive nodes and recurrence score that was less than 26 who seemed to benefit. Right? So that was a clearer population. I think for the premenopausal population, there was benefit for chemotherapy across all of those patients, and I think that this has raised a few questions including: Is that benefit specifically due to the ovarian function suppression effect? Is there a direct effect as well?

I also think the important thing in terms of how people utilize the test—You know, I think in the postmenopausal women it's clear that there's benefit in checking the test. I also think for the premenopausal patients there's prognostic utility, meaning if your recurrent score is 22 and you're premenopausal and if your recurrent score is 2 and you're premenopausal, your risk, your absolute risk, is different, meaning that your absolute benefit from chemotherapy—even though across that range if you look at the hazard ratio it's similar—the absolute benefit is higher. So I also think it does help to inform the conversation.

Dr. Chalasani:
Yeah. So, can you comment on for premenopausal women, if their recurrence score does come back at two or things, you know, like on the study at this time, they would have been recommended endocrine therapy. Correct?

Dr. Kalinsky:
Yeah. So, for the patients with recurrence score 0 to 25 and you're premenopausal, we saw that, you know, across the different increments that there was a numeric benefit with the addition of chemotherapy. I think that there's a likelihood that we could be overtreating patients, and, you know, that's the last thing that we want to do. And also, I just want to mention in RxPONDER that it was about a third of the patients. So I think that when we're talking about this with patients, we have to keep in mind the risk. And I will say that if you have a patient who's in front of you—Let's say you have a 40-year-old woman with a one centimeter tumor, one lymph node involved, and you check her recurrence score and it comes back as two, is it appropriate to think about having the conversation about doing ovarian function suppression plus hormonal therapy as opposed to the discussion about chemotherapy? I think it's something we need to talk about risks and benefits and things we do and don't know with patients. I also think that this in general remains a gray area.

Dr. Chalasani:
So, on that note, you know, in the context of COVID-19 pandemic and there were, like, significant delays for surgeries there has been a significant uptake in the neoadjuvant treatments that we use for patients. So, infrequently, all of us come across in tumor board where patients are hormone receptor-positive, HER2-negative. In the node-negative setting, we tend to have a little bit more flexibility, but let's say we see a patient in hormone receptor-positive, HER2-negative, node-positive setting. Given this, is this something you would use these assays to determine if we can use chemotherapy in the neoadjuvant setting?

Dr. Kalinsky:
Yeah. You know, this I think is the hardest thing to discuss in tumor board, and what I generally say—and maybe we'll remove COVID from this equation. We learned some things since then, but I think the question is about the role of genomics in the subtype of breast cancer. And I think whenever I have the conversation about giving therapy before surgery, the question is, 'Well, what is the intent of doing the treatment before? What are you trying to achieve? Are you trying to improve surgical outcomes? Do you need to debulk the axilla? Are you aiming to have breast conservation therapy? Is the tumor very large and you really need to see a significant response? So I think there is that nuance in there.

If you look at the ASCO/CAP guidelines about the genomic assays, there was no consensus, that there were clear guidelines to suggest the utility of checking these assays in the neoadjuvant setting just because some of these studies are smaller studies and have not—are not necessarily associated with long-term outcomes.

Dr. Chalasani:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and I'm speaking with Dr. Kevin Kalinsky about the RxPONDER trial. And to bring all these assays together or things, can you tell us the role of the recurrence score assays and the other genomic assays that we have currently available in clinical practice, and where you would use the different assays?

Dr. Kalinsky:
I appreciate the question because it is important to reiterate that this is not the only assay that's commercially available. There are

others like the 70-gene MammaPrint assay. There is EndoPredict. There's Prosigna. We also have, for instance, the Breast Cancer Index, which is an assay that looks over—at H/I, and when that's utilized, it's really in the context of determination of extending endocrine therapy or not.

I will say, in terms of large randomized studies, we have data from the MINDACT study, which was designed differently, which was looking at clinical risk and genomic risk and was looking—The primary endpoint was based upon looking at that high clinical risk and low genomic risk population. What I will say is that they have additional follow-up in these cohorts in the MINDACT cohort. And if you look at 8-year distant metastasis-free survival, again in that high-clinical-risk and low-genomic-risk population, I will say that in the overall population couldn't find a population who seemed to benefit from chemotherapy, but the same story is playing out here. If you look at the patients who are age 50 or less, there was a 5 percent absolute difference in distant metastasis-free survival at eight years in that high-clinical-risk, low-genomic-risk population in those who got chemo or not as opposed to the patients who were greater than 50 years of age.

So, what I will say just about utilization of assays, you know, in those guidelines that I mentioned, they also reiterate the point that one shouldn't necessarily check more than one assay, so I would stick with the assay that you determine to check or you opt to check, but the other thing that I would also say about if one is utilizing the 70-gene MammaPrint assay, I would think about it in the context of the MINDACT study.

Dr. Chalasani:
So, one of the other things that we frequently come across when they're discussing is how they're using, you know, the recurrence scores or the MINDACT—you know, the scores when they have the high genomic is the type of chemotherapy to use, if you could just comment on the types or what, if there is any correlation between the scores and the chemotherapy you would recommend.

Dr. Kalinsky:
There are not data that suggest that recurrence score can be predictive of specific chemotherapy. Right? I will say in RxPONDER we did look back and look to see patients who got non-anthracycline and anthracycline-based treatment However, when we did this exploratory post-hoc analysis, we couldn't see a difference between those who received a taxane versus not.

Dr. Chalasani:
These are all great insights that you have shared, but I want you to give the final word, Dr. Kalinsky. Do you have any other takeaways that you would like to leave our audience with today?

Dr. Kalinsky:
I think that, for me, the question and the future of utilization of assays to determine treatment I think that in future podcasts we are likely to be talking about blood markers, including circulating tumor DNA. And, you know, there are studies that are starting and/or about to start that's going to be looking at the clinical utility of these assays, not just to determine prognostic risk but also if you change the treatment whether you can decrease the likelihood of recurrence.

Dr. Chalasani:
Great. With those final thoughts in mind, I want to thank my guest, Dr. Kevin Kalinsky, for sharing his findings from the RxPONDER trial and insights on chemotherapy for patients with hormone receptor-positive, HER2-negative, node-positive breast cancer. Dr. Kalinsky, it was great having you on the program today.

Dr. Kalinsky:
Thanks, 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.