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HER2-Low mBC and NCCN Guidelines: Providing Optimal Care for Patients

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm your host, Dr. Charles Turck, and joining me to discuss how we can apply the current National Comprehensive Cancer Network, or NCCN, breast cancer guidelines to HER2-low breast cancer in practice is Dr. Paolo Tarantino. Dr. Tarantino is a Medical Oncologist and Advanced Research Fellow in the Breast Oncology Program at Dana Farber Cancer Institute at Harvard Medical School. Dr. Tarantino, thanks for being here today.

Dr. Tarantino:
Thank you so much for having me.

Dr. Turck:
Now before we dive in, Dr. Tarantino, let's start with some background. What are some key factors that differentiate HER2-low breast cancer from HER2-negative breast cancer?

Dr. Tarantino:
I think it's important to remember that HER2-low is a very new definition, that for a long time, we'd be only considering breast cancer to be either HER2-positive or HER2-negative, depending on the presence of either HER2 amplification that FISH or overexpression and immunohistochemistry. And then recently, in 2022 we saw the results of a trial that really changed practice, also in the way we define HER2. DESTINY-Breast04 established the role of trastuzumab deruxtecan and then antibody drug conjugate, not only for HER2-positive but also for HER2-low breast cancer. And now we define, and also the NCCN guidelines define HER2-low as immunohistochemical score of 1+ or 2+ with negative ISH assay, meaning that it's not tumors that have the amplification of HER2, and they are driven by HER2, but it's tumors that still have some expression of HER2, and so we call them HER2-low. And usually the HER2-negative tumors that are not HER2-low, now we tend to call them HER2-0 because they have an immunohistochemical score of zero for HER2.

Dr. Turck:
Now you mentioned a little bit about the NCCN guidelines and how they currently support the use of fam-trastuzumab deruxtecan-nxki in patients with HER2-low metastatic breast cancer. So would you tell us a little bit more about that recommendation?

Dr. Tarantino:
Well, after the DESTINY-Breast04 trial that showed how trastuzumab deruxtecan improved both progression-free survival and overall survival among patients with HER2-low metastatic breast cancer that had received prior endocrine treatment and chemotherapy, basically, the NCCN guidelines rapidly were updated in order to include these options for patients that had once again metastatic breast cancer that had received at least one line of chemotherapy previously, or also patients that have recurred rapidly after adjuvant chemotherapy. And this is usually the way we currently consider the use of trastuzumab deruxtecan after at least one line of chemotherapy, and so in the chemotherapy pretreated setting, although recently we saw a press release showing that another trial, DESTINY-Breast06, may take T-DXd even earlier, before the use of chemotherapy. Although we still haven't seen the results from this trial.

And I think one important thing to remember is that this applies both for patients with hormone receptive-positive metastatic breast cancer, but also triple negative. So you just need to identify some HER2-low expression, 1+ or 2+, ISH negative, and the NCCN guidelines allow to utilize trastuzumab deruxtecan.

Dr. Turck:

So with all this in mind, what's the optimal sequencing of treatments for HER2-low breast cancer?

Dr. Tarantino:
So sequencing remains actually very complex, mostly because things are moving very fast, which is good news. We know that it's important to see more options becoming available to treat our patients with metastatic breast cancer and with cancer in general.

The thing is that when you have several phase 3 trials reading out, you often don't have comparative data. And so for instance, we have positive data with trastuzumab deruxtecan in DESTINY-Breast04, we have positive data with sacituzumab govitecan in two different phase 3 trials, ASCENT and TROPiCS-02, and we have also positive data from another Trop2 ADC that is datopotamab deruxtecan in TROPION-Breast01 trial. And all of these novel antibody drug conjugates that deliver topoisomerase inhibitors have shown to improve progression-free survival compared with physician choice of chemotherapy. However, we don't know really how they perform compared to each other and not also one after the other. And so in clinical practice, we often sequence antibody drug conjugates, in particular trastuzumab deruxtecan and sacituzumab govitecan, but we are not sure of what is the right sequence.

In hormone receptive positive disease, what we tend to do is follow the population of patients that were enrolled in the trials. And so since in DESTINY-Breast04, patients that received a median of one prior line of chemotherapy, we tend to utilize T-DXd a little bit earlier than sacituzumab govitecan, which was instead tested after a median of three prior lines of chemotherapy.

In triple negative disease instead, it's a little different because sacituzumab govitecan was tested in a large phase 3 trial, the ASCENT study, whereas T-DXd was tested in a smaller population, included in DESTINY-BREAST04 with HER2-low disease and triple negative disease.

So in general, we discussed with the patients bringing up the different side effects profile, and also the activity data that we have. And another point that helps is the presence or absence of intracranial disease because we know that patients that have brain metastases, which are an important unmet need can derive benefit from antibody drug conjugates. But we have more data with trastuzumab deruxtecan compared to sacituzumab govitecan. So in general, it's good to have this problem, to have several options, and we are learning day by day how to best sequence them. But for the moment, the best thing is to follow the trial designs and understand what populations were enrolled in the different studies.

Dr. Turck:
And when selecting a therapeutic approach, how do you keep a patient's unique needs in mind while also considering the NCCN recommendations? How do you balance those considerations?

Dr. Tarantino:
So that's a great question. And I think, first of all, it's extremely important to look at the comorbidities of the patients because sometimes those can really guide the treatment choice. And so for instance, trastuzumab deruxtecan is associated with approximately 15 percent rate of interstitial lung disease, an inflammation of the lungs. And in the trials that tested T-DXd, such as DESTINY-Breast04 and other DESTINY trials, patients were excluded if they had prior interstitial lung disease requiring steroids. And so for a patient that has established interstitial lung disease or other severe lung comorbidities, I may think of a different treatment option. Whereas, for a patient that instead had issues with cytopenias, neutropenia with prior treatment lines, or also GI issues, actually, sacituzumab govitecan may be more problematic as a treatment line. And finally, for patients with peripheral neuropathy, I may want to give something different from eribulin or taxane.

So I think really the comorbidities can help, but also of course, the preferences. And so for instance, one important side effect of some of these treatments is alopecia. And we know that some of these treatments have got extremely high rates of alopecia. Sacituzumab govitecan, most of the patients that receive the drug will experience grade 2 complete alopecia, whereas trastuzumab deruxtecan, this rate is more around the 20 to 30 percent. And we're also now studying cold caps to understand if we can prevent alopecia. We hope to present data by the next year.

But in general, I think assessing the preferences of the patient's, understanding what are the comorbidities, and also what the patient can access at every time point is extremely important in order to make the best decisions at every time point.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr Charles Turck, and I'm speaking with Dr. Paolo Tarantino about the latest guidelines for managing HER2-low breast cancer.

Now I'd like to switch gears a bit, Dr. Tarantino, and focus on a real-world case. Would you tell us about a time when you used the NCCN guidelines and how you selected a treatment option for your patient with HER2-low breast cancer?

Dr. Tarantino:

Absolutely. I think NCCN guidelines are extremely helpful to discuss with the patients the available options at every point. And I'm thinking of a patient that I saw last week with hormone receptor-positive metastatic breast cancer that was also HER2-low. And the patient had received prior treatment with endocrine treatment, CDK4/6 inhibitors capecitabine and trastuzumab deruxtecan, and we had to choose the next line of treatment for this patient. And if you look at the NCCN guidelines, what they recommend is that among patients that received two prior lines of chemotherapy or systemic therapy, and we can consider T-DXd somewhat a chemotherapy and systemic therapy, then you can utilize sacituzumab govitecan.

And the thing is that we don't have good data on the sequencing of ADCs, of T-DXd, and sacituzumab govitecan. And we know that these two agents carry a similar chemotherapy, a topoisomerase inhibitor. And so I discussed with the patient, of course, the availability and the indication of sacituzumab govitecan in this setting based on TROPiCS-02 trial. But at the same point, I discussed about the lack of sequencing data with the disease, the fact that we have just only some real-world case series for the moment, although we are about to open a trial the TRADE-DXd randomized phase 2 trial, which will answer this question.

And so besides sacituzumab govitecan, I discussed other options that are included by the NCCN guidelines. There are basically several options of chemotherapy, including eribulin, taxanes. And after wide discussions about the activity of each option and side effect profile, the patient preferred to try a different line of something that may be different from TOP1 ADC. And so we did eribulin, and we left sacituzumab govitecan for the next line of treatment doing basically what is considered by some the sandwich strategy, meaning that not doing the ADCs one after the other, but putting something different in between. And there is not complete agreement on this, but this is why I think it's extremely important to have an open discussion, a shared decision-making, and really the NCCN guidelines can be helpful in this setting.

Dr. Turck:
Thanks for sharing that case with us, Dr. Tarantino. And before we close, what other advice would you give our colleagues on incorporating the NCCN guidelines into practice?

Dr. Tarantino:
I think what is extremely important is to remember that these guidelines are dynamic, so they evolve, and they're based on the latest evidence. But at the same time, things are moving so fast that it's important to remember to look at them again after some time, just because there may have been some major change, and also to keep updated on real-world data. Because, I think, in the past, with several clinical trials that took some time and produced data, let's say, in a slow manner, it was easier to make decisions based on clinical trials alone. But more and more real-world data is allowing us to understand what happens when you sequence different drugs in a modern population. And so I think looking at the latest update of the NCCN guidelines, looking also at all the small footnotes that sometimes are very precious to understand how to interpret them, but also looking at the latest real-world data to see how ADCs perform in the real world, how they perform one after the other. And also what are the toxicities in the real world of these drugs? Because we know that real-world patients are different from the ones in clinical trials. All of this can really help to make for decision-making in clinical practice, always discussing with the patient and having a shared decision-making in clinical practice.

Dr. Turck:
Those are great insights to end our discussion. And I want to thank my guest, Dr. Paolo Tarantino, for his perspective and advice on navigating HER2-low breast cancer care. Dr. Tarantino, it was great having you on the program.

Dr. Tarantino:
Thank you very much, Dr. Turck. Thank you everybody for attending this program.

Dr. Turck:
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