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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Navigating New Waters in HER2+ mCRC: Selection of the Optimal Targeted Regimen, a Case-Based Approach

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Dr. Strickler:
Hi, I'm John Strickler from Duke University Medical Center in Durham, North Carolina. Today, I'm going to speak about navigating new waters in HER2 positive metastatic colorectal cancer selection of the optimal targeted regimen, a case-based approach.

Currently, we're fortunate we have a number of anti-HER2 therapeutic options available to us in the clinic. All of these options are validated in nonrandomized or randomized phase 2 studies. Each regimen available to us has different levels of evidence behind it, different levels of side effects, and factors to be aware of.

Lapatinib and trastuzumab is available – was initially tested in patients with HER2 overexpressing, so 2+ FISH positive or IHC 3+ disease. And this this - there are certain factors that would lead us to give lapatinib/trastuzumab versus an antibody drug conjugate. Trastuzumab/pertuzumab is another regimen that's been well validated in the MyPathway study and is currently in our national guidelines. This has been validated in patients with HER2 positivity by any assay. Similarly, tucatinib and trastuzumab has been validated in both nonrandomized and a randomized study in patients who are HER2 positive by any CLIA certified assay, whether it be IHC or FISH, NGS - or NGS. And then finally, trastuzumab/deruxtecan has been validated in DESTINY-CRC01 in patients who are - who have HER2 IHC 2+, FISH positive, or IHC 3+ disease.

Now there are certain genomic factors, clinical genomic factors that may influence the choice. Both trastuzumab/deruxtecan, and tucatinib/trastuzumab have data in other cancers showing that they're active against brain metastases. There has been some data that suggests that trastuzumab/deruxtecan may have a signal of safety around interstitial lung disease or pneumonitis. So that therapy would be less desirable in that setting where there some pre-existing interstitial lung disease. And additionally, both tucatinib/trastuzumab, trastuzumab/deruxtecan, and pertuzumab/trastuzumab have high activity that specific against HER2 as a target. Finally, trastuzumab/deruxtecan is noteworthy in that it is the only therapy that's shown activity in patients who have already progressed on a prior anti-HER2 therapy.

Now, as mentioned, there are certain adverse event profiles or side effect profiles that are associated with each regimen. Both lapatinib/trastuzumab and pertuzumab/trastuzumab are known to cause diarrhea as their most common side effects, the lapatinib as a nonspecific anti-HER2 inhibitor, may cause more rash. Tucatinib/trastuzumab is highly selective against HER2 which likely minimizes the rash side effect but diarrhea, and it's manageable, grade 1 or grade 2 levels, can be seen. And then finally, trastuzumab/deruxtecan because it's linked to chemotherapy is known to have greater levels of fatigue, nausea, and myelosuppression. It also is associated with interstitial lung disease or pneumonitis.

So I'm going to start now with a case and explain how anti-HER2 therapies were used and how the decision was made to select certain

therapies. In this first case, this is a 58-year-old male with metastatic rectal cancer. He initially presented with lower gastrointestinal bleeding. Rectal biopsy confirmed adenocarcinoma, and CT showed extensive liver metastases. Now the original panel at that time did not include HER2 as part of that panel, and he was found to have KRAS, NRAS, and BRAF wild-type disease that was microsatellite stable. He progressed on first-line FOLFOX and Bevacizumab, and then finally progressed on maintenance chemotherapy. He progressed rapidly on second-line FOLFIRI/panitumumab, and then progressed rapidly on a third-line regorafenib-based clinical trial.

So at that time, a liquid biopsy was obtained to examine mechanisms of resistance and to find actionable alterations, hopefully for off-label treatments or trials.

As shown here, on the left, the blood-based profile show that the patient's blood had HER2 amplification in it, suggesting that the patient's tumor was HER2 positive. Because HER2 testing was not initially included in tissue in the next generation sequencing panel, we went back and looked at HER2 amplification by the standard IHC and FISH, and found that this tumor in fact was HER2 overexpressing and highly amplified for HER2. Now at the time, this was many years ago, the patient - we had limited options in the clinic and there was initial data showing activity for the combination of lapatinib and trastuzumab, so that's what was chosen for his treatment.

And on the left, we see a CT scan of a baseline image with those dark spots representing some of his disease burden in the liver. And after six cycles of lapatinib and trastuzumab, he had rather dramatic response to treatment. His family members were so happy that he was able to get performance status back and able to participate in activities that he was unable to do before he started. Now because this was lapatinib, which is a non-selective HER2 inhibitor, he did struggle with diarrhea and rash and that led to some reduction of his dose of lapatinib, but he stayed on it for some period of time before eventually progressing.

Next in case 2, this is a more recent example of a 49-year-old male with metastatic colon cancer. He presented to his local emergency room with a large bowel obstruction. And CT scan showed extensive liver metastases as well as abdominal lymphadenopathy, and he was found to have a partially obstructing mass in a sigmoid colon. He received an emergent surgery, diverting colostomy, and due to poor performance status, he declined palliative chemotherapy. And at that time molecular testing was ordered. And we can see the results of that commercial NGS profile on the right, where we see APC mutation, TP53 mutation, and ERBB2, otherwise known as HER2 amplification.

So the patient had his original diagnosis of metastatic colon cancer, and when he was – and he declined systemic chemotherapy due to concerns that his performance status was inadequate to tolerate that type of treatment. He was willing, however, to take targeted therapies. And at the time, we were able to access trastuzumab and pertuzumab. He initially did well on the treatment, had some diarrhea, but unfortunately developed new brain metastases. Those brain metastases were treated. And then we've made the switch from pertuzumab, which is a monoclonal antibody tucatinib, which is a tyrosine kinase inhibitor. And the reason why tucatinib was selected is that this is a small molecule that's known to penetrate the central nervous system and cover brain metastases. So the patient then went on trastuzumab and tucatinib, which he tolerated very well.

On our left, we see his imaging of his liver before initiating treatment with tucatinib and trastuzumab. This is at the time that he was diagnosed with brain metastases and was on trastuzumab/pertuzumab. His baseline CEA was 1,724. After 3 months of tucatinib and trastuzumab, he had a deep response to treatment with significant reduction in the size of his liver metastases, and he's had no recurrence of his brain metastases while on tucatinib and trastuzumab.

I will point out that the main treatment-related side effect since he's been on tucatinib has been diarrhea. This has been manageable. On rare occasions he takes Imodium but he has not required a dose reduction due to the diarrhea, and his quality of life is excellent.

Thank you very much for joining me for this activity.

Announcer:
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