CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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Sequencing Strategies in the Management of Metastatic Colorectal Cancer With *HER2* Amplification

Kanwal P. S. Raghav, MBBS, MD
Associate Professor
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

H&O How common is *HER2* amplification in metastatic colorectal cancer (CRC)?

KR *HER2* amplification is seen in approximately 2% to 3% of unselected patients with CRC. The amplification rate is higher among patients with *RAS* wild-type disease, at approximately 5% to 6%, and lower among patients with *RAS*-mutant disease, at approximately 1% to 2%. The amplification rate does not appear to differ between early-stage disease and metastatic disease.

H&O What special treatment options are available for patients who have *HER2*-amplified metastatic CRC?

KR *HER2* amplification is a negative predictor of response to anti–epidermal growth factor receptor (EGFR) therapy, so we generally avoid cetuximab (Erbitux, Lilly) and panitumumab (Vectibix, Amgen) in these patients. We do not have any large, prospective studies proving that these patients do not benefit from anti-EGFR therapy, but a review of retrospective studies shows that benefit is unlikely. Aside from that, patients with *HER2*-amplified metastatic CRC are eligible for the other therapies that are available to patients with wild-type *HER2*.

The US Food and Drug Administration (FDA) has not approved any targeted agents specifically for use in *HER2*-amplified metastatic CRC, but guidelines from the National Comprehensive Cancer Network (NCCN) provide several options for patients with pretreated disease, and for patients with previously untreated disease who are not candidates for intensive therapy. The first is dual anti-HER2 therapy with trastuzumab and lapatinib, the second is dual anti-HER2 therapy with trastuzumab and pertuzumab (Perjeta, Genentech), and the third and most recent is monotherapy with the antibody-drug conjugate trastuzumab deruxtecan (T-DXd; Enhertu, Daiichi-Sankyo/AstraZeneca). All 3 of these therapies are for use in *HER2*-amplified tumors that are also *RAS* and *BRAF* wild-type.

H&O What studies served as the basis for the NCCN recommendations?

KR In the multicenter, phase 2 HERACLES trial, researchers administered trastuzumab and the HER2/EGFR inhibitor lapatinib to 27 patients with previously treated, HER2-positive tumors. After a median follow-up of 94 weeks, the objective response rate (ORR) was 30%, including 1 patient with a complete response, 7 patients with a partial response, and 12 with stable disease.

The MyPathway study, which is a phase 2a basket study, included 57 patients with previously treated, *HER2*-amplified metastatic CRC who received a combination of trastuzumab and pertuzumab. After a median follow-up of 7.3 months, the ORR was 32%, including 1 complete response and 17 partial responses.

The multicenter, phase 2 DESTINY-CRC01 trial administered T-DXd to 78 patients with HER2-expressing, *RAS/BRAF* wild-type, unresectable or metastatic CRC

that had progressed on at least 2 prior lines of treatment. After a median follow-up of 27.1 weeks, the ORR among the 53 patients with a high level of HER2 expression (cohort A) was 45.3%, with 1 complete response and 23 partial responses. The median progression-free survival among these patients was 6.9 months. The ORR was similar among the 20.5% of patients who had received prior anti-HER2 therapy, at 43.8%.

H&O What additional research is being done?

KR Early data from the open-label, phase 2 MOUNTAINEER study, which Dr John Strickler presented at the 2021 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, supported the use of trastuzumab and tucatinib (Tukysa, Seagen). This combination is also being evaluated in a randomized, phase 2 expansion of the MOUNTAINEER study (NCT03043313).

The randomized, phase 2 S1613 study from the Southwest Oncology Group is comparing dual anti-HER2 therapy using trastuzumab/pertuzumab vs the anti-EGFR/cytotoxic chemotherapy regimen of cetuximab/irinotecan (NCT03365882). This study has a planned enrollment of 130 participants.

In addition, the randomized, phase 2 DESTINY-CRC02 study is further evaluating the use of T-DXd (NCT04744831). This study is planning to enroll 120 participants.

H&O What should be the first line of treatment in *HER2*-amplified metastatic CRC?

KR The first step across all lines of treatment is to consider enrolling the patient in a clinical trial if possible. Beyond that, the first line therapy of therapy for most of these patients is a combination of bevacizumab—unless contraindicated for a reason such as cardiac disease, hemorrhage, or thrombosis—and cytotoxic chemotherapy. Although steps are being taken toward evaluating HER2-directed therapies in the first line for patients with CRC, this is not the standard of care.

H&O What would you say the second line of treatment should be?

KR If no clinical trial is available, I would move to one of the HER2-directed therapy options.

H&O What would you say for the third line of treatment?

KR I would continue with HER2-directed therapy in the third line. Research in breast cancer and gastric cancer has established that if we change our strategy, HER2-directed therapies continue to work. It is perfectly reasonable to use dual anti-HER2 therapy in the second-line setting and then go on to use an antibody-drug conjugate. A subgroup analysis of DESTINY-CRC01 showed equivalent and comparable responses to T-DXd in patients who had received prior anti-HER2 therapy and in those who had not. Again, the preferred option is always a clinical trial.

H&O Is T-DXd effective in *RAS*-mutant patients?

KR We do not have the answer to that question, but preclinical evidence and the mechanism of action suggest that it should be. In addition, the DESTINY-CRC01 study was a study for patients with *RAS* wild-type disease, but an analysis of circulating tumor DNA that was presented at the most recent ASCO meeting revealed that some patients did have *RAS* mutations, and responses appeared comparable between the 2 groups. The design of the DESTINY-CRC02 study should give us the answer to that question because *RAS*-mutant patients are eligible to participate.

H&O Is T-DXd effective in patients with a low level of HER2 expression?

KR That depends on the definition of a low level of expression. If a low level of HER2 expression is defined as 1+ or 2+ without amplification—as in cohorts B and C in DESTINY-CRC01—then T-DXd does not appear to show any efficacy in CRC. This is in contrast to breast cancer, in which T-DXd has shown activity in women with breast cancer who have a low level of HER2 expression. I think that the target still holds promise, but we will need to readdress this question later when new treatments or combinations of treatments are available.

H&O What adverse effects are associated with dual HER2-directed therapy?

KR The combination of trastuzumab and lapatinib that was studied in the HERACLES trial had a favorable adverse event profile. Even though tyrosine kinase inhibitors such as lapatinib are a bit harder to tolerate than monoclonal antibodies such as trastuzumab, adverse events, which included fatigue, skin rash, and increased bilirubin, occurred in only 22% of patients. We do have concerns about heart issues with trastuzumab, but no significant heart issues occurred in this study.

In the MyPathway study, 37% of patients who received trastuzumab and pertuzumab experienced a grade 3 or 4 adverse event, with the most common being low

potassium levels and abdominal pain. Compared with the other therapies that we use in CRC, HER2-directed therapies are well tolerated.

> Although we have made headway in developing anti-HER2 therapies, we need to make treatments better.

H&O What adverse events are associated with T-DXd?

KR The major adverse event that we need to worry about with T-DXd is interstitial lung disease, which affected 5 patients (6%) and led to 2 deaths (2.6%) in DESTINY-CRC01. Apart from that, side effects are minimal. Grade 3 or higher adverse events, which occurred in 61.5% of patients, consisted mainly of decreased neutrophil counts and anemia. So, this is a fairly well-tolerated treatment, considering the response it is able to achieve in a population with highly refractory disease.

H&O What should the next steps in research be?

KR The bottom line is that although we have made headway in developing anti-HER2 therapies, this is not the kind of headway we should be satisfied with—we need to make treatments better. The response rates to current HER2-directed treatments are between 30% and 40%, so many patients are left without benefit.

Another problem is the lack of FDA approval for these indications, despite their inclusion in the NCCN guidelines. Our goal should be to make these therapies more accessible, which means directing patients toward clinical trials rather than giving them off-label therapy. Patients who have metastatic CRC with *HER2* amplification are rare, so I would encourage all oncologists to find such patients early in the course of their treatment continuum and refer them to centers engaging in clinical trials. We are always available to see any of these patients at our center.

Disclosure

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Suggested Readings

ClinicalTrials.gov. S1613, trastuzumab and pertuzumab or cetuximab and irinotecan hydrochloride in treating patients with locally advanced or metastatic HER2/neu amplified colorectal cancer that cannot be removed by surgery. https://clinicaltrials.gov/ct2/show/NCT03365882. Identifier: NCT03365882. Updated January 10, 2022. Accessed January 13, 2022.

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