CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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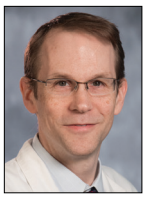
The Emerging Role of Antibody-Drug Conjugates in Metastatic Colorectal Cancer



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H&O How well is colorectal cancer (CRC) suited to antibody-drug conjugate (ADC) therapy, in comparison with other solid tumors?

JS It has been historically challenging to develop ADCs for CRC, for several reasons. The first limiting factor has been the difficulty in identifying suitable targets—those that are present in CRC tumors but not found in normal tissue. A second limiting factor has been that CRC is notoriously heterogeneous with respect to target expression, and that heterogeneity can sometimes limit the effectiveness of targeted therapeutics. A final limiting factor has been the fact that CRC often contains compensatory pathways and backup mechanisms to rescue tumors from both cytotoxic chemotherapy and targeted therapy.

H&O Which target antigens are showing the most promise for the CRC-directed ADCs currently in development?

JS A few targets are especially promising. We already have US Food and Drug Administration (FDA) approval for one ADC in CRC: the anti–human epidermal growth factor receptor 2 (anti-HER2) ADC trastuzumab deruxtecan, also known as T-DXd (Enhertu, Daiichi-Sankyo/AstraZeneca). T-DXd has FDA approval for immunohistochemistry (IHC) 3+ HER2-overexpressing advanced solid tumors, including CRC. Additionally, promising data have been generated with anti–c-MET ADCs. One example is telisotuzumab adizutecan, also known as ABBV-400 or Temab-A, which consists of the c-MET–targeting monoclonal antibody telisotuzumab conjugated to adizutecan, a novel topoisomerase 1 (TOP1) inhibitor payload. Temab-A has shown encouraging levels of activity—particularly in patients with higher levels of c-MET expression. In a phase 1 study of patients with advanced solid tumors and progression on standard therapies, the overall response rate among 113 patients who had CRC treated with Temab-A and were evaluable ranged from 6% in the 32 patients on the lowest dose, 1.6 mg/kg every 3 weeks, to 24% in the 41 patients on the highest dose, 3.0 mg/kg every 3 weeks.[1] Among the 40 patients with CRC who received Temab-A at a dose of 2.4 mg/kg every 3 weeks, the ORR was 18% overall and 37.5% among patients with higher c-MET expression. On the basis of these results, a phase 2 study is evaluating Temab-A in combination with 5-fluorouracil, folinic acid, and bevacizumab for the second-line treatment of metastatic CRC (NCT06107413), and a phase 3 trial is comparing Temab-A vs TAS-102 plus bevacizumab in patients with chemorefractory metastatic CRC and high c-MET expression (NCT06614192).

More recently, we have seen some published results with an ADC against carcinoembryonic antigen–related cell adhesion molecule 5 (CEACAM5) and a TOP1 inhibitor payload. In the phase 1 PROCEADE-CRC-01 trial of the agent precemtabart tocentecan among 40 heavily pretreated patients with irinotecan-refractory metastatic CRC, 2 patients had a partial response.[2] This trial is still recruiting patients. Other targets of interest for ADC drug development have included mesothelin,[3] epidermal growth factor receptor and its ligands,[4,5] and HER3.[6]

I would like to emphasize the importance of selecting an ADC with the optimal drug payload for CRC. Most of the favorable results observed to date have been in studies that used a TOP1 inhibitor payload. Initial drug development efforts that used a microtubule inhibitor payload, such as monomethyl auristatin, had notably less activity. Additionally, linker-payload stability is critical for CRC because early release of the cytotoxic payload into the circulation may increase toxicity and reduce the ability to administer active doses. Finally, the ratio of cytotoxic payload to antibody (drug-antibody ratio) has required refinement. All these factors are critical to the success of the ADC strategy.

> We may eventually have ADCs that are so active and well tolerated that they can be advanced into early lines of treatment.

H&O How do you assess the challenge of tumor heterogeneity when selecting ADC targets in metastatic CRC?

JS Molecular heterogeneity is a feature of many gastrointestinal tumors, including CRC. To account for this heterogeneity, patient selection is critical. For patients with CRC, we have learned that higher levels of target expression predict lower levels of heterogeneity. For example, HER2 expression is heterogeneous when it is low (1+) or intermediate (2+), but HER2 expression tends to be uniform at the highest level (3+). This uniform expression may explain why T-DXd is active in metastatic CRC primarily when HER2 expression is high (IHC 3+). I expect that we will observe a similar relationship between clinical activity and target antigen expression with other ADCs.

H&O What biomarkers beyond target antigen expression should guide ADC patient selection?

JS Before the recent approval of T-DXd for patients with HER2 IHC 3+ solid tumors, we typically relied on DNA-based biomarkers for determining the best course of treatment for CRC. These biomarkers include *KRAS* mutations, *NRAS* mutations, *BRAF* V600E mutations, *HER2* alterations, and other rare alterations. Microsatellite instability (MSI) or mismatch repair (MMR) expression is an exception to this rule because it can be assessed by protein expression (IHC) or DNA (polymerase chain reaction or next-generation sequencing). Given the notable challenges of developing ADCs for CRC, it is increasingly clear that effective patient selection based on validated biomarkers is critical. We will need to explore gene signatures and other markers in the tumor microenvironment to better understand predictors of treatment response.

H&O What are the key toxicity concerns with ADCs in patients who have CRC, and how do those differ from the toxicity concerns with traditional chemotherapy?

JS The cytotoxic payload of an ADC may lead to myelosuppression, anemia, thrombocytopenia, and neutropenia, all of which are common with both ADCs and traditional chemotherapy. In addition, ADCs carry some unique toxicities as a class. We have seen elevated rates of interstitial lung disease or pneumonitis with some ADCs, particularly T-DXd. The mechanism of this toxicity is not well understood, but it may occur through off-target payload release. Alveolar macrophages in the lung may absorb the cytotoxic payload, leading to cellular toxicity and an inflamed microenvironment.

H&O Where do ADCs fit into the current sequencing of treatments for metastatic CRC?

JS We currently use T-DXd in the later-line treatment of patients with chemotherapy-refractory disease, but it does not have to be used in that way. Given their favorable tolerability and activity, ADCs could be placed anywhere in the treatment continuum. As we continue to develop these new therapeutics, I suspect that we will attempt to replace conventional chemotherapy with ADCs, particularly as we acquire a better understanding of the risk-to-benefit balance. It is quite possible that one day we will use ADCs as first- or second-line therapy, as opposed to waiting until a patient's disease has progressed on multiple lines of therapy.

H&O How do you evaluate ADC efficacy in microsatellite stable (MSS) vs microsatellite instability–high (MSI-H) CRC?

JS That is important because we are increasingly recognizing MSI-H tumors as biologically distinct from MSS tumors. MSI-H cancers need to be treated on an immunotherapy pathway. For these patients, ADCs may have less to offer. However, most patients with metastatic CRC—approximately 95%—have MSS cancers. Here, immunotherapy has a more limited role, and targeted therapies and ADCs are a focus of drug development.

Chemotherapy is typically active in early lines of therapy for metastatic MSS CRC, but this activity wanes with cumulative exposure. ADCs are typically evaluated as a salvage strategy for patients with disease progression on multiple lines of chemotherapy. However, we may eventually have ADCs that are so active and well tolerated that they can be advanced into early lines of treatment. More research is needed before we will be able to sequence ADCs before traditional cytotoxic chemotherapy.

H&O How might ADCs be combined with immunotherapy in future CRC treatment paradigms?

JS We think about ADCs as a cytotoxic chemotherapy strategy, so until now, we have not routinely tested them with immunotherapy. The challenge we have with MSI-H CRC is that immunotherapies are so active that it is very difficult to improve them. An intriguing strategy would be to pair immunotherapy with an ADC in patients with MSS CRC, in which immunotherapy is less active. One approach includes targeting an immunosuppressive cell population with an ADC while stimulating the immune system with an immune checkpoint inhibitor. This therapeutic strategy would require an understanding of which cell populations drive immunotherapy resistance, and a target antigen that is preferentially expressed in the "cold" tumor immune microenvironment. If successful, this therapeutic strategy could convert immunotherapy-resistant tumors into responsive tumors, thereby addressing a significant unmet need.

H&O What additional research would you like to see conducted?

JS To date, identification of an effective chemotherapy payload for the ADC has been critical. Several ADCs were active in other solid tumors, but ineffective in CRC. Now we have TOP1 inhibitor payloads, which are active in CRC. However, even more active chemotherapy payloads may exist. Additionally, the optimal drug-to-antibody ratio may require greater refinement. Finally, novel targets are needed. We need not only to identify the best targets for CRC but also to define the level of expression that is critical to predicting response. Once that novel ADC demonstrates safety and activity, we will then need predictive biomarkers that are easy to measure and are reliable indicators of treatment response. Blood-based biomarkers are particularly convenient and offer advantages for tumors with heterogeneous target expression. It is also important to highlight the unique biology of each tumor type. It is possible that these predictive biomarkers will need to be customized to the tumor type, line of therapy, and site of metastases.

H&O What do you see happening over the next few years when it comes to the use of ADCs in metastatic CRC?

JS ADCs are demonstrating promising activity in patients with metastatic CRC, and we already have our first FDA-approved therapy. We are likely to see more approved therapies in the chemotherapy-refractory setting, and my expectation is that these therapies will eventually be advanced into earlier lines. It is also possible that we could use ADCs in the adjuvant or molecular residual disease–positive space. As this therapeutic class enters the CRC treatment landscape, we will have to incorporate predictive biomarkers into our testing algorithms, and to ensure that testing is supported. Finally, ADCs may offer novel strategies to target immunosuppressive cell populations and enhance the activity of immunotherapies. Much work remains to be done, but I remain hopeful that ADCs will become an important therapeutic strategy for patients with CRC.

Disclosures

Dr Strickler has served in a consultant or advisory role with AbbVie, Amgen, Astellas, AstraZeneca, Bayer, BeOne Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Cytovation, Daiichi-Sankyo, Eli Lilly, GE HealthCare, GSK, Incyte, Ipsen, Johnson & Johnson, Jazz Pharmaceuticals, Leap Therapeutics, Merck, Natera, Pfizer, Pheon Therapeutics, Quanta Therapeutics, Roche/Genentech, Regeneron, Sanofi, Taiho Oncology, Takeda, Xilio Therapeutics, and Triumvira Immunologics (stock options), and has received research funding or done contracted research for AbbVie, Amgen, Apollo Therapeutics, Bayer, BeOne Medicines, Daiichi-Sankyo, Eli Lilly, GSK, Leap Therapeutics, Novartis, Pfizer, Quanta Therapeutics, Revolution Medicines, and Roche/Genentech (payment to institution).

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