CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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When to Use Triplet Chemotherapy as First-Line Treatment in Metastatic Colorectal Cancer

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H&O What are the options for first-line treatment in metastatic colorectal cancer (CRC)?

CC First, I want to emphasize that chemotherapy still matters a great deal in metastatic CRC. Unlike certain other solid malignancies, in which chemotherapy can often be omitted in favor of targeted therapy or immunotherapy to achieve good control, chemotherapy remains an important backbone for the first-line treatment of patients with metastatic colorectal cancer.

The main choices for patients with metastatic CRC are chemotherapy plus bevacizumab, or chemotherapy plus an anti–epidermal growth factor receptor (EGFR) monoclonal antibody.

Regarding chemotherapy plus bevacizumab, different intensities of chemotherapy can be used. Chemotherapy may consist of monotherapy with 5-fluorouracil (5-FU) or oral capecitabine; doublet chemotherapy with leucovorin/5-FU/oxaliplatin (FOLFOX), capecitabine/oxaliplatin (XELOX), or leucovorin/5-FU/irinotecan (FOLFIRI); or triplet chemotherapy with leucovorin/5-FU/oxaliplatin/irinotecan (FOLFOXIRI).

We have good evidence supporting the use of an anti-EGFR monoclonal antibody in combination with a chemotherapy doublet. Preliminary data highlight very interesting response and resection rates with reduced-dosage triplet chemotherapy when combined with an anti-EGFR monoclonal antibody. The data are not as robust as for doublet chemotherapy, however, and the added value of the intensified chemotherapy backbone is still under investigation.

H&O How do practitioners decide between bevacizumab and anti-EGFR agents?

CC We do have some criteria to guide us in this decision. For example, anti-EGFR agents are the best choice in patients who have *RAS* and *BRAF* wild-type left-sided tumors—meaning that they originate distally to the splenic flexure of the colon—and are fit to receive a chemotherapy doublet. Bevacizumab is usually the best targeted agent to use in other patients.

H&O Why is the choice of the first-line chemotherapy regimen so important in these patients?

CC The choice of first-line treatment in the setting of metastatic CRC is crucial. Curative treatment is possible in a small percentage of patients with metastatic disease, especially if their disease spread is limited to the liver. Case series support the idea that optimal chemotherapy can in some cases convert unresectable disease to resectable disease, allowing for radical resection of metastatic lesions and leading to a long disease-free interval.

Even if first-line treatment is unable to make the disease resectable, it may control disease enough to allow other systemic regimens or locoregional treatments to work. Failing to control disease up front may make it impossible to put into action all the other weapons we have in our quiver.

H&O Which patients with metastatic CRC should receive first-line triplet therapy with FOLFOXIRI plus bevacizumab?

CC Triplet therapy with FOLFOXIRI plus bevacizumab is not appropriate for patients older than 75 years, and those between 71 and 75 years old are eligible to receive

triplet chemotherapy only if their general condition is very good, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0. And of course, patients should not receive any drug that is contraindicated for them. All of these factors are important when considering whether to use FOLFOXIRI plus bevacizumab as first-line treatment.

Triplet chemotherapy is a very good option for patients who have aggressive tumors. For example, the data suggest that more-intensive treatment benefits patients with *BRAF*-mutated metastatic CRC, who have a very poor prognosis. Up-front exposure to a more-intensive treatment may be able to counteract the intrinsic aggressiveness of the disease.

Treatment with FOLFOXIRI plus bevacizumab should not be limited to just those who have *BRAF*-mutated metastatic CRC, however. Patients with right-sided tumors, which are extremely aggressive, also may benefit from this regimen—especially given that anti-EGFR monoclonal antibodies appear to have little effect on these tumors.

I think that FOLFOXIRI plus bevacizumab is a very good regimen to use in an effort to convert metastatic CRC from unresectable to resectable. However, the subgroup analyses of TRIBE (Combination Chemotherapy and Bevacizumab as First-Line Therapy in Treating Patients With Metastatic Colorectal Cancer) and TRIBE-2 (FOLFOXIRI Plus Bev Followed by Reintroduction of FOLFOXIRI Plus Bev at Progression Versus FOLFOX Plus Bev Followed by FOLFIRI Plus Bev in mCRC)—the strongest evidence-based trials on which to base our decisions—do not suggest a specific subgroup in which the triplet combination is the best choice. Overall, when feasible, FOLFOXIRI plus bevacizumab may be a preferred option for most fit patients with a right-sided and/or *RAS*- or *BRAF*-mutant tumor and an ECOG performance status of 0.

H&O How many patients are potentially eligible for a triplet regimen?

CC At least 40% or 50% of patients fall into one of the categories that is well suited to treatment with a triplet regimen. Of course, patients who are elderly are not eligible.

H&O Could you further describe the research on triplet therapy in these patients?

CC TRIBE and TRIBE-2 are the largest studies on FOLFOXIRI/bevacizumab in patients with metastatic CRC. We have strong evidence from the TRIBE study and from other smaller, phase 2 randomized trials that the triplet regimen of FOLFOXIRI plus bevacizumab is able to achieve progression-free survival of approximately 1 year in patient populations enriched for *RAS* and *BRAF* mutations, who have a poor prognosis. This regimen is highly active and leads to remarkable overall survival (OS).

To provide more detail, the TRIBE study compared FOLFOXIRI plus bevacizumab vs FOLFIRI plus bevacizumab as first-line treatment for metastatic CRC. The study showed an advantage for the triplet in terms of response rate, PFS, and OS, along with an increased incidence of diarrhea, mucositis, and neutropenia. Fortunately, clinicians have tools for managing these side effects, whether they are caused by a doublet or triplet regimen. Based on these results, FOLFOXIRI/bevacizumab was added to all major international guidelines on metastatic CRC as an option for first-line treatment.

The results of TRIBE led to an additional question: Is the up-front administration of the 3 drugs superior to a preplanned strategy of exposure to the same drugs in a sequential manner? Specifically, researchers were worried about the efficacy and feasibility of treatments after progression and wanted to know whether using the 3 drugs up front might be more effective than using 2 of the drugs as first-line treatment and introducing the third drug in second-line. The phase 3 TRIBE-2 study was designed to answer this question. For this study, participants with previously untreated metastatic colorectal cancer were randomly assigned to receive first-line FOLFOX/bevacizumab followed by FOLFIRI/bevacizumab after disease progression, or FOLFOXIRI/bevacizumab followed by reintroduction of the same regimen after disease progression. In order to properly assess the efficacy of the whole first- and second-line strategy, the primary endpoint of the study was PFS2, defined as the time from randomization until the second evidence of disease progression on any treatment given after first progression, or death. The trial met its primary endpoint, showing a significant advantage with the up-front use of the triplet plus bevacizumab in terms of PFS2, and consistent benefit in terms of response rate, R0 resection rate, and first PFS. Interestingly, no difference in second PFS (ie, the time between first and second disease progression) was evident in the overall population. In contrast, among patients able to receive the preplanned second-line treatment (ie, FOLFIRI plus bevacizumab in the control arm and FOLFOXIRI plus bevacizumab in the experimental arm), the triplet plus bevacizumab provided a small advantage in terms of response rate, disease control rate, and second PFS, at the price of an increased incidence of neurotoxicity. At the preliminary OS analysis, a significant benefit from up-front FOLFOXIRI plus bevacizumab was also observed.

These results strengthen the findings of the TRIBE study; they confirm the usefulness of the triplet regimen as an up-front treatment option in eligible patients with metastatic CRC, and are definitely reassuring about the efficacy of subsequent treatments when starting the therapeutic route with the triplet plus bevacizumab.

H&O What other concerns besides side effects exist with triplet therapy regimens?

CC A major concern that oncologists have with using FOLFOXIRI/bevacizumab treatment is that if they use it as first-line treatment and then the disease progresses, they will not have anything to offer their patients. Are other treatment regimens effective as second-line treatment?

The results of the TRIBE and TRIBE-2 studies are reassuring in this regard. If the advantage provided by the triplet had only occurred when it was used as first-line treatment, we would have seen a significant advantage in PFS but not in OS. In fact, TRIBE and TRIBE-2 showed that the triplet regimen was associated with an advantage in both PFS and OS. In other words, achieving meaningful disease control at the beginning of treatment may have a meaningful effect on longer-term outcomes.

H&O What other relevant studies are being conducted?

CC The Gruppo Oncologico del Nord Ovest (GONO), which includes more than 50 sites throughout Italy, is now conducting the AtezoTRIBE study (FOLFOXIRI + Bev + Atezo vs FOLFOXIRI + Bev as First-line Treatment of Unresectable Metastatic Colorectal Cancer Patients). The goal of this study is to examine the use of immunotherapy in patients with microsatellite-stable metastatic CRC, which normally does not respond to immunotherapy. Could combining immunotherapy with other treatment make it valuable in patients with microsatellite-stable tumors? Specifically, could bevacizumab make immunotherapy more effective in resistant patients by promoting lymphocytic infiltration of the tumor?

We plan to enroll 200 patients in this phase 2 study. Patients are randomly assigned to FOLFOXIRI/bevacizumab with or without atezolizumab (Tecentriq, Genentech). I wish to emphasize that the addition of immune checkpoint inhibitors to FOLFOXIRI/bevacizumab is experimental, and should not be used outside of clinical trials.

Regarding FOLFOXIRI plus anti-EGFR agents, this combination used to be considered too toxic because of a high incidence of adverse events, especially gastrointestinal events. But with reductions in the doses of 5-FU and irinotecan, the combination with an anti-EGFR agent has become feasible. Several phase 2 trials have been conducted using reduced-dose FOLFOXIRI in combination with the anti-EGFR agents cetuximab (Erbitux, Lilly) or panitumumab (Vectibix, Amgen), in which the combination led to tumor shrinkage that translated into very good rates of secondary resection of metastatic lesions.

Despite this research, it remains unclear whether using triplet rather than doublet chemotherapy is beneficial in combination with an anti-EGFR agent in molecularly selected patients (ie, those more likely to derive benefit from the targeted agent itself). For this reason, a phase 3 Italian trial called TRIPLETE (First Line mFOLFOXIRI + Panitumumab vs mFOLFOX + Panitumumab in *RAS* and *BRAF* WT Metastatic Colorectal Cancer Patients) is randomly assigning patients with *RAS* and *BRAF* wild-type metastatic colorectal cancer to receive standard treatment with modified FOLFOX6 plus panitumumab, or an experimental regimen with modified FOLFOXIRI plus panitumumab.

Another study, called AVETRIC, will be looking at FOLFOXIRI with cetuximab or the anti–programmed death 1 inhibitor avelumab (Bavencio, EMD Serono/Pfizer). This phase 2 single-arm study, which will likely begin in the fall, will investigate whether exploiting the antigen-exposure role of up-front chemotherapy and the ability of cetuximab to induce both antibody-dependent cellular cytotoxicity and immunogenic cell death may pave the way for the efficacy of the checkpoint inhibitor in metastatic colorectal cancer.

Disclosure

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Suggested Readings

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