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Recognizing Patient Subtypes in Late-line Colorectal Cancer for Selection of Targeted Therapy

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WHEN TREATING METASTATIC COLORECTAL CANCER (MCRC), it is important to consider the uniqueness of each patient and of selecting targeted therapies that are most appropriate for specific patient populations. Although a class of medications, such as anti–epidermal growth factor receptor (anti-EGFR) antibodies and anti–vascular endothelial growth factor (anti-VEGF) antibodies, may be considered a group of agents by some clinicians and managed care professionals, the differences among the included agents must not be overlooked, as responses can vary among patient populations. Recognizing these differences can help clinicians understand the nuances of treatments within these classes and help managed care professionals carefully consider these agents when making formulary decisions that may affect the available choices for therapy in many patients with metastatic cancer.

Left Versus Right Tumors and Clinical Outcomes

Clinical outcomes depending on the origin of the primary tumor have been analyzed in retrospective studies. For instance, in a study of cetuximab in combination with chemotherapy, rates of overall survival (OS) and progression-free survival (PFS) in patients whose mCRC originated from the right side of the colon were 55% lower than in those whose tumors originated from the left side. Those whose cancer originated in the left side of the colon also had longer survival. Both patient populations had wild-type *KRAS* mCRC with an origin of either left- or right-sided colon. Median survival lengths were 33.3 months and 19.4 months in patients with mCRC that originated from the left side and right side, respectively.[1] Therefore, combination of cetuximab and chemotherapy had more benefit in patients with left-sided colon cancer.[2]

It is important to note the limitations of these findings, however. For example, the mechanism by which right- and left-sided colon cancers responded to the therapy are not fully understood and some studies showed a greater prevalence of a *KRAS* mutation in cancers originating in the right side of the colon.[2] Also, the poorer prognosis in patients with right-sided tumors may be explained by the reduced diagnostic delay compared with left-sided tumors, as left-sided tumors may produce symptoms, such as bleeding, earlier than the right-sided tumors.[1] Although more research is required, these results show important differences among populations of patients with colorectal cancer, which may have relevance for treatment selection.

Targeted Therapy Agents: Anti-EGFR Antibodies

Although surgery is widely considered the most effective treatment for early-stage colorectal cancer, for later stage colorectal cancer, surgery plus chemotherapy and targeted treatment are the preferred options. Because cancer is a heterogenous set of diseases, targeted approaches are needed to supplement treatment with standard chemotherapy.

Targeted therapies continue to be developed and used in the management of colorectal cancer. One such group of therapies are the anti-EGFR antibodies. Routinely used for the treatment of mCRC, these agents include cetuximab (Erbitux) and panitumumab (Vectibix).[3] Cetuximab and panitumumab elicit activity by inhibiting various signaling pathways of EGFR, thus inhibiting the cell proliferation in the G1 phase.[4] The amino acid sequence of cetuximab is partially murine in origin, encoding an IgG1 chimerised monoclonal antibody, whereas panitumumab is a fully humanized IgG2 antibody, which accounts for differences in the frequency of infusion reactions between agents.[5]

In one noninferiority study, based on prespecified noninferiority criteria, OS was similar among patients receiving panitumumab or cetuximab. However, this study was limited to patients with disease progression after prior chemotherapeutic treatment and does not represent the full range of patients with mCRC. Further research is needed to answer the clinical relevance of these findings across the entire treatment course and to analyze the use of these agents in earlier lines of therapy and in combination with such regimens as folinic acid-fluorouracil-irinotecan (FOLFIRI) or folinic acid-fluorouracil-oxaliplatin (FOLFOX).[6]

CRYSTAL study

FOLFIRI is an option for first-line chemotherapeutic treatment of mCRC. As a more recent approach to treating colorectal cancer, targeted therapies are being studied as monotherapy or as combination therapy with standard chemotherapy. For example, in a study of patients with wild-type *KRAS* receiving a combination of cetuximab and FOLFIRI, the combination showed a benefit over FOLFIRI alone, both in terms of PFS and OS.[3]

Although cetuximab increases the survival rate in patients with wild-type *KRAS* compared with best supportive care and standard therapy with the FOLFIRI regimen alone, cost-effectiveness must also be evaluated to expand the utilization of the targeted therapy. The CO.17 trial, which was conducted in Canada, assessed the cost-effectiveness of cetuximab through the incremental cost-effectiveness ratio (ICER), which itself was assessed via the ratio of cost per life-year gained and cost per quality-adjusted life-year gained.[7]

Results of the CO.17 study show that when cetuximab was used in patients with wild-type *KRAS*, it had a lower ICER than best supportive care compared with all other patients in the trial. This indicates that avoiding the use of cetuximab in patients with a mutated *KRAS* gene might reduce healthcare expenditures compared with provision of cetuximab to patients with wild-type *KRAS* only.[7] These results show the importance of targeted therapeutic options for select patient groups.

Targeted Therapy Agents: Anti-VEGF antibodies

Bevacizumab, a humanized monoclonal anti-VEGF antibody, has been associated with fewer dermal side effects than anti-EGFR antibodies and may thus be better tolerated by some patients.[8] However, the results of several studies suggest that use of bevacizumab plus fluorouracil/leucovorin with or without irinotecan has shown clinical improvement in both OS and PFS in patients with colorectal liver metastases (CLM).[3]

In treatment of mCRC, bevacizumab was first approved in 2004 for use in combination with fluorouracil and leucovorin as first-line therapy in mCRC.[9] This approval was based on study results showing that in patients with mCRC who failed first-line therapy with irinotecan-based regimens, the combination of bevacizumab and FOLFOX4 improved PFS and OS compared with FOLFOX4 monotherapy.[10] Evidence for the addition of bevacizumab is stronger for patients receiving it with irinotecan-based regimens than with oxaliplatin-based regimens.[9] As a result, although the evidence shows some benefit of bevacizumab plus FOLFOX4, use of this VEGF inhibitor in combination with oxaliplatin-based therapy is not currently considered first-line treatment for patients with CLM.[3]

Targeted Therapy Agents: Newer agents

Newer targeted therapy agents approved for use in mCRC include regorafenib (Stivarga), ramucirumab (Cyramza), and ziv-aflibercept (Zaltrap).

Regorafenib is a broad inhibitor of protein kinases, including kinases involved in tumor angiogenesis regulation, oncogenesis, and tumor microenvironment. Compared with best supportive care alone, regorafenib improves OS in patients with mCRC who previously received all available standard therapies. Regorafenib also has shown benefit in OS and PFS in patients with both colon cancer and rectal cancer; however, on both OS and PFS, the benefits of regorafenib appeared to be greater in patients with colon cancer versus patients with rectal cancer. Additionally, study results of patients from eastern Europe failed to demonstrate any difference between regorafenib and supportive care on PFS, which may have clinical relevance in treatment.[11] »

Ramucirumab is a fully humanized monoclonal antibody that elicits antitumor activity by inhibiting VEGF, thereby inhibiting cell signaling and proliferation.[12] In the RAISE study, which evaluated treatment with ramucirumab versus placebo in patients with mCRC receiving second-line FOLFIRI after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine, adding ramucirumab to FOLFIRI improved both OS and PFS relative to placebo.[13]

Ziv-aflibercept is a recombinant fusion protein that exerts anti-VEGF activity by binding to VEGF, thus preventing VEGF ligands from binding to endogenous receptors. In one study, the addition of ziv-aflibercept to FOLFIRI provided OS and PFS benefits in patients with mCRC who had received oxaliplatin-containing therapy. Ziv-aflibercept is the first agent to show an OS benefit in this patient population.[14]

Understanding Targeted Therapies Beyond Class Effects

Targeted therapies are part of a movement toward personalized medicine and more effective cancer treatment. The results of several phase 3 studies have shown PFS and OS benefits with the use of targeted treatments, either with chemotherapy alone or in patients who received prior therapies.[15] However, to avoid overtreating patients, it is important to consider available regimens, patient-specific factors, and any background therapies. To treat patients in an evidence-based manner, it is important to consider treatment options based on the specific population for which a treatment has been studied rather than extrapolating data for one agent within a therapeutic class to all agents within that class.

Unlike chemotherapy, which acts broadly and indiscriminately, targeted therapies have the potential for less toxicity to healthy cells. To better manage cancer, which is characterized by heterogeneous tumors, targeted therapies may represent the most promising set of treatments. This is because cancers are prone to mutations, which may give rise to subclones that have an ever-changing set of molecular characteristics, even within a single patient. Effective targeted therapies should be used in the context of an understanding and comprehension of the generic and molecular characteristics of the tumor as well as of the important differences between treatments in the specific populations studied.[16] ■

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