Guidlines and Population Considerations in Colorectal Cancer

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TARGETED THERAPIES ARE A SET of therapies that block the spread of cancer by interfering with specific molecular targets involved in its growth and progression.[1] These treatments differ from traditional chemotherapy, which exerts nonspecific effects on all fast-dividing cells within the body.[1] By contrast, targeted therapies help selectively inhibit pathways, interfering with cell functions that play a role in cancer cell growth and survival. In cancer treatment, targeted therapies are becoming increasingly important, although their use has been largely confined to later-line therapy in many cancer types, including in the treatment of colon cancer.

Where Targeted Therapy Falls in Colon Cancer Guidelines

Colon cancer and its corresponding treatments vary by the stage, from I through IV. Treatment of stage I and II colon cancer is focused on surgical therapy with either colectomy or lymphadenectomy.[2] In some stage II cancers in which cancers has spread to nearby sites, adjuvant chemotherapy, such as folinic acid + fluororuracil + oxaliplatin (FOLFOX) or capecitabine + oxaliplatin (CAPEOX), may be used.[3] Stage III tumors are generally treated with surgery and adjuvant chemotherapy. Chemotherapeutic regimens may include FOLFOX, folinic acid + fluorouracil + irinotecan (FOLFIRI), CAPEOX, flurouracil + leucovorin + oxaliplatin (FLOX), capecitabine, or 5-fluorouracil + leucovorin.[3]

> **Targeted therapies help selectively inhibit pathways, interfering with cell functions that play a role in cancer cell growth and survival.**

Currently, use of targeted therapies is limited to patients with stage IV metastatic colon cancer. In stage IV colon cancer, patients who do not benefit from chemotherapy alone may experience improved response if targeted therapy is added to treatment. However, treatment choice may depend on whether or not cancer is resectable. Chemotherapeutic regimens in the metastatic setting may include FOLFOX, CAPEOX, FOLFIRI, FLOX, capecitabine, or fluorouracil + leucovorin.[3] For patients with unresectable tumors, chemotherapy with or without bevacizumab, chemotherapy plus panitumumab, or chemotherapy plus cetuximab may be considered. Notably, use of EGFR inhibitors, such as panitumumab or cetuximab, is preferable for patients with left-sided tumors with wild-type *KRAS* or *NRAS* genes. Selection of EGFR inhibitors should also take into account *BRAF V600E* mutations, which may limit effectiveness.[2]

Targeted Therapies' Phase III Trials

Six targeted therapies are currently used for the management of advanced colon cancer: bevacizumab, cetuximab, panitumumab, regorafenib, ramucirumab, and aflibercept. Mechanistically, bevacizumab, ramucirumab, and aflibercept are anti-VEGF therapies, while cetuximab and panitumumab are anti-EGFR therapies. Unlike other available treatments, regorafenib is a multi-kinase inhibitor, which inhibits VEGF, among other factors. See **Table**[4-9] for a list of the drugs, doses, and trial results.[4-9]

Bevacizumab

Bevacizumab was the first VEGF inhibitor approved for colon cancer. A trial by Hurwitz et al analyzed survival rates in patients receiving bevacizumab with irinotecan, fluorouracil, and leucovorin (IFL), versus IFL alone. Eligible patients included adults aged 18 years or older with good Eastern Cooperative Oncology Group (ECOG) performance status (defined as ECOG 0 to 1) and a life expectancy of greater than 3 months. Every 2 weeks, patients received either IFL with bevacizumab 5 mg/kg intravenously (IV), or IFL plus placebo. At the end of the trial, overall survival (OS) was longer in the group receiving bevacizumab plus IFL versus IFL alone (20.3 months vs 15.6 months; $P<.001$). The median duration of progression-free survival (PFS) was improved for patients receiving bevacizumab plus IFL versus IFL alone (10.6 vs 6.2 months; $P<.001$).[4]

TABLE 1. Key Study Findings With Targeted Therapies for Colon Cancer[4-9]

TARGETED THERAPY DRUG	RESULTS
Bevacizumab (Avastin)	—OS of bevacizumab plus IFL compared with IFL alone (20.3 vs 15.6 months; P <.001). —PFS of bevacizumab plus IFL compared with IFL alone (10.6 vs 6.2 months; P <.001)
Cetuximab (Erbitux)	—Median time to disease progression comparing cetuximab plus an irinotecan-based regimen with cetuximab alone (4.1 vs 1.5 months; P <.001).
Panitumumab (Vectibix)	—46% reduction in the relative risk of progression was observed in patients receiving panitumumab compared with those receiving best supportive care (HR, 0.54; 95% CI, 0.44-0.66).
Ramucirumab (Cyramza)	—For patients receiving ramucirumab plus FOLFIRI, median OS duration was 13.3 months, while patients receiving FOLFIRI alone had a median OS duration of 11.7 months (P = .0219).
Aflibercept (Zaltrap)	—OS was longer in patients receiving aflibercept plus FOLFIRI compared with patients receiving placebo plus FOLFIRI (13.80 vs 11.93 months; P = .0008). —The difference in median PFS also favored the aflibercept plus FOLFIRI treatment arm compared with placebo plus FOLFIRI (6.80 vs 4.53 months; P <.0001).
Regorafenib (Stivarga)	—OS was longer in the regorafenib arm than in the placebo arm (6.4 vs 5.0 months; P = .0052). —PFS was also longer in the regorafenib arm: 1.9 months versus 1.7 months in the placebo arm (P <.0001).

FOLFIRI indicates folinic acid + fluorouracil + irinotecan; HR, hazard ratio; IFL, irinotecan + fluorouracil + leucovorin; OS, overall survival; PFS, progression-free survival.

Cetuximab

Cetuximab is an anti-EGFR targeted treatment approved for use in colon cancer. Cunningham et al evaluated the safety and efficacy of cetuximab used in combination with an irinotecan-based regimen versus cetuximab alone. In this trial, patients with stage IV metastatic colon cancer expressing *EGFR*, refractory to irinotecan therapy, were randomized in a 2:1 ratio to receive either an irinotecan-based regimen with cetuximab or cetuximab monotherapy. In this trial, the median time to disease progression for the cetuximab and irinotecan combination therapy group was 4.1 months, while for the cetuximab group it was 1.5 months (P <.001).[5]

Panitumumab

Like cetuximab, panitumumab is an anti-EGFR targeted therapy approved for the treatment of colon cancer. VELOUR, an open-label phase III study, examined panitumumab plus best supportive care versus best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. Although no OS benefit was detected, a significant 46% reduction in the relative risk of progression was observed in patients receiving panitumumab compared with those receiving best supportive care (hazard ratio, 0.54; 95% CI, 0.44-0.66).[6]

Ramucirumab

Ramucirumab is an anti-VEGF targeted therapy for the treatment of stage IV metastatic colon cancer. RAISE, a phase III study, compared use of ramucirumab plus second-line FOLFIRI versus FOLFIRI alone in patients with metastatic colorectal cancer that progressed during or after first-line chemotherapeutic treatment.[7] For patients receiving ramucirumab plus FOLFIRI, median OS duration was 13.3 months, while patients receiving FOLFIRI alone had a median OS duration of 11.7 months (P = .0219).[7]

Aflibercept

Aflibercept is also an anti-VEGF targeted therapy that was studied in the VELOUR trial. Aflibercept plus FOLFIRI versus FOLFIRI alone were evaluated in the second-line treatment of metastatic colorectal cancer. Patients had metastatic colorectal cancer and failed first-line treatment on a regimen that included oxaliplatin, or had relapsed during or within 6 months of completion of a oxaliplatin-containing regimen. They were randomly assigned to receive either aflibercept plus FOLFIRI or placebo plus FOLFIRI. At the trial's end, OS was longer in patients receiving aflibercept plus FOLFIRI compared with patients receiving placebo plus FOLFIRI (13.80 vs 11.93 months; P = .0008). The difference in median PFS also favored the aflibercept plus FOLFIRI treatment arm compared with placebo plus FOLFIRI (6.80 vs 4.53 months; P <.0001).[8]

Regorafenib

Regorafenib is a multikinase inhibitor that affects several signaling pathways; it blocks VEGF signaling. Regorafenib is intended for use after other lines of therapy for colon cancer »

have already failed. Grothey et al designed a trial to assess the safety and efficacy of regorafenib in patients with metastatic colorectal cancer who had progressed after having received standard therapies. Patients were aged 18 years or older, had an ECOG performance status of 0 or 1, and had a life expectancy of at least 3 months. Patients were randomized in a 2:1 ratio to receive either regorafenib orally once a day or placebo. At the end of the trial, OS was longer in the regorafenib arm than in the placebo arm (6.4 vs 5.0 months; $P = .0052$). PFS was also longer in the regorafenib arm: 1.9 months versus 1.7 months in the placebo arm ($P < .0001$).[9]

ASPECCT Trial

Few trials in gastrointestinal cancers compare the efficacy and safety of targeted therapies within the same class; ASPECCT is 1 such trial. This noninferiority trial was designed to compare outcomes with panitumumab and cetuximab, 2 anti-EGFR targeted therapies. In this clinical study, limited to patients with chemotherapy-refractory metastatic colorectal cancer, panitumumab was shown to be noninferior to cetuximab in all aspects evaluated, including OS, PFS, objective response rate, and safety outcomes. The median OS times were 10.2 months with panitumumab and 9.9 months with cetuximab ($P = .0002$ for noninferiority). Median PFS time was 4.2 months with panitumumab and 4.4 months with cetuximab. Finally, objective response rates with panitumumab and cetuximab were 22% and 19.8%, respectively. Additionally, the safety profiles of the 2 medications were found to be similar.[10]

Cost Effectiveness Analysis Comparing Panitumumab and Cetuximab

An economic analysis using data from the original ASPECCT trial was performed to determine if there were cost benefits in using panitumumab versus cetuximab, as the medications were proven noninferior. The researchers concluded that panitumumab was superior to cetuximab in projected drug acquisition costs, mode of administration, and safety outcomes, for patients with wild-type *KRAS* who have metastatic colorectal cancer. Panitumumab was also found to have better outcomes in terms of projected life-years (1.072 vs 1.051 life-years), and a larger gain in quality-adjusted life-years (QALYs) (0.736 vs 0.726 QALYs). The projected cost savings per patient was $9468.[11]

Although these findings seem to support use of panitumumab over cetuximab, several limitations of the economic analysis must be addressed prior to forming that conclusion. This analysis was based on the results of ASPECCT, a noninferiority trial.[11] In the ASPECCT trial, patients were required to have an ECOG score of 0 to 2, and to have adequate renal and hepatic function, which is not representative of many patients with metastatic colorectal cancer.[10] Furthermore, the analysis is based on a semi-Markov model, in which simulated groups of patients continually transition across different health states. These simulated outcomes may not reflect the actual patient outcomes or cost savings. Importantly, there was only a marginal difference of 0.01 QALY between agents (0.736 for panitumumab and 0.726 for cetuximab).[11] Finally, the adverse effect profile included in costs was largely focused on infusion reactions, which are known to vary across treatment centers, which may detract from the universality of study findings. Although findings from this analysis may suggest that panitumumab is more cost-effective, more research is required before reaching this conclusion universally.[11]

Comparison Between Bevacizumab (Avastin) and Cetuximab (Erbitux)

Several trials, including the KRK-0306 study, have compared bevacizumab and cetuximab. In this trial, investigators evaluated outcomes in patients with *KRAS*-mutated tumors receiving either bevacizumab plus FOLFIRI or cetuximab plus FOLFIRI. Overall response rates were 44% in the FOLFIRI plus cetuximab combination therapy group versus 48% in the FOLFIRI plus bevacizumab combination therapy group. The median PFS duration was 7.5 months in patients receiving cetuximab versus 8.9 months in patients receiving bevacizumab. The median OS duration was 22.7 months with cetuximab and 18.7 months with bevacizumab. Although it is known that cetuximab is not effective in mutated *KRAS* tumors, from this trial, it was clear that bevacizumab does not perform any better than cetuximab in this patient group. Researchers reported a greater incidence of acneiform exanthema in patients receiving cetuximab, and a higher rate of grade 3/4 hypertension among those receiving bevacizumab.[12]

A similar study evaluated bevacizumab versus cetuximab in combination with chemotherapy as first-line treatment in Chinese patients with metastatic colon cancer, and cetuximab and bevacizumab were found to have similar efficacy. The median PFS rates were 10.6 and 8.7 months in the bevacizumab and cetuximab groups, respectively ($P = .316$). The median OS was 27.7 months with bevacizumab versus 28.3 months with cetuximab ($P = .510$). The overall response rate for cetuximab versus bevacizumab was also not significantly different (53.5% vs 43.1%; $P = .108$).[13] In a trend, however, patients receiving cetuximab-based triplet therapy had a higher conversion rate to resectability compared with patients receiving bevacizumab-based triplet therapy (46.3% vs 28.8%; $P = .058$).[13] In addition, in patients with peritoneal metastasis, bevacizumab proved superior

to cetuximab in both PFS (9.6 vs 6.1 months; $P<.001$) and OS (26.3 vs 12.7 months; $P=.006$).[13]

In a third study, FIRE-3, which compared FOLFIRI in combination with either bevacizumab or cetuximab in patients with metastatic colorectal cancer, rates of PFS were found to be similar between the 2 treatment arms: 10.0 and 10.3 months for patients treated with cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI, respectively ($P=.55$). Median OS rates were also found to be similar between the 2 treatment arms (28.7 vs 25.0 months in the cetuximab and bevacizumab arms, respectively; $P=.017$). However, in an analysis limited to patients with wild-type *RAS*, there was an advantage in OS with cetuximab compared with bevacizumab (33.1 vs 25.6 months, $P=.011$).[14]

In the fourth and final study comparing bevacizumab and cetuximab in patients with wild-type *KRAS* colorectal cancer, median OS was 30.0 months in patients receiving cetuximab plus chemotherapy and 29.0 months in patients receiving bevacizumab plus chemotherapy ($P=.08$).[15] Rates of median PFS times were also similar between the cetuximab and bevacizumab groups, with durations of 10.5 months and 10.6 months, respectively ($P=.45$).[15] Finally, the respective response rates for cetuximab and bevacizumab were 59.6% and 55.2% ($P=.13$).[15]

Conclusion

Targeted therapy includes a novel group of treatments that may help improve outcomes for patients with metastatic colon cancer, as monotherapy, and in some cases, when used in combination with chemotherapy. Targeted therapies are different from chemotherapy in that they target specific receptors that may promote cancer growth and survival. Because these drugs are reserved for patients with advanced cancer, few head-to-head trials have been performed. However, it is important to recognize the available evidence and possible differences among treatments both across and within treatment classes. ■

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