

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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The Value and Effectiveness of Angiogenesis Inhibitors for Colorectal Cancer



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H&O What is the mechanism of action for angiogenesis inhibitors?

APV There are a variety of angiogenesis inhibitors, but fundamentally, they all act on factors that promote the growth of blood vessels that are necessary for cancers to proliferate and grow. The hypothesis is that cancers can grow to a certain size without blood flow, but after a certain point, they require an adequate blood supply to access the oxygen and nutrients they need to keep growing. Therefore, if the growth of blood vessels is blocked, the growth of the tumor also is blocked.

H&O What angiogenesis inhibitors are currently US Food and Drug Administration (FDA)-approved for colorectal cancer?

APV The definition of an angiogenesis inhibitor varies, but there are multiple FDA-approved drugs for colorectal cancer that interfere with angiogenesis in some way. The classic drug is bevacizumab (Avastin, Genentech), which is an anti-vascular endothelial growth factor (VEGF) antibody that blocks the binding of VEGF to its receptor (VEGFR) and thereby slows tumor growth. Bevacizumab is approved for use in numerous malignancies in combination with chemotherapy. For colorectal cancer specifically, it is approved for multiple stages, including for metastatic tumors as first-line therapy in combination with chemotherapy.

Ziv-aflibercept (Zaltrap, Sanofi/Regeneron) is an angiogenesis inhibitor approved for use in combination

with folinic acid, 5-fluorouracil, and irinotecan (FOLFIRI) in patients with metastatic colorectal cancer that has progressed following an oxaliplatin-containing regimen. Ziv-aflibercept is known as a VEGF trap; it inhibits angiogenesis by binding to VEGF, but the mechanism of action is distinct from that of bevacizumab.

Another angiogenesis inhibitor was approved for colorectal cancer in April 2015: ramucirumab (Cyramza, Lilly). This drug is a monoclonal antibody against VEGFR2 and is approved for use in combination with FOLFIRI for patients with metastatic colorectal cancer who have progressed during or after therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

Regorafenib (Stivarga, Bayer) is a multikinase inhibitor that at least partially inhibits angiogenesis by blocking VEGFR2 and other growth factor pathways. This drug is approved in metastatic colorectal cancer for patients who have previously been treated with FOLFIRI and an anti-VEGF therapy.

These approved drugs interfere with angiogenesis through pathways that are defined by VEGF. There are many other angiogenesis inhibitors, but not all are approved in colorectal cancer.

H&O How effective was bevacizumab for treating colorectal cancer in clinical trials?

APV Bevacizumab was first approved by the FDA in 2004 for metastatic colorectal cancer as first-line therapy in combination with chemotherapy. Published by Dr Hurwitz and colleagues, this double-blind trial randomly assigned

813 patients to receive chemotherapy (irinotecan, 5-fluorouracil, and leucovorin [IFL]) with or without intravenous bevacizumab. The patients who received bevacizumab had an average of 4 months longer progression-free survival (6.2 months vs 10.6 months; hazard ratio [HR], 0.54; $P < .001$) and 5 months longer overall survival (15.6 months vs 20.3 months; HR, 0.66; $P < .001$). The response rates were also higher in the patients with vs without bevacizumab (44.8% vs 34.8%, respectively; $P = .004$). The patients from this study had very advanced disease; other trials have found that bevacizumab is not effective in patients with less than stage 4 disease. Bevacizumab was later approved for use in metastatic colorectal cancer as a second-line treatment and in combination with fluoropyrimidine-based chemotherapy as first-line treatment.

H&O Could you describe the clinical trial for ziv-aflibercept approval in colorectal cancer?

APV In August 2013, ziv-aflibercept was approved by the FDA in combination with the FOLFIRI regimen of chemotherapy for patients with metastatic colorectal cancer who have progressed following an oxaliplatin-containing regimen. Approval was based on a double-blind placebo-controlled multicenter phase 3 trial published by Dr Van Cutsem and colleagues. This trial randomly assigned 1226 patients to receive FOLFIRI with ziv-aflibercept or placebo every 2 weeks until disease progression or unacceptable toxicity. Patients receiving ziv-aflibercept had a statistically significant increase in overall survival compared with those receiving placebo (HR, 0.82; 95% CI, 0.71-0.94; $P = .0032$). The median overall survival was 13.5 months vs 12.06 months, respectively. Progression-free survival was significantly longer in the ziv-aflibercept group than in the placebo group (HR, 0.76; 95% CI, 0.66-0.87; $P < .0001$) with a median of 6.9 months vs 4.7 months, respectively. The response rates also were significantly higher in patients receiving ziv-aflibercept (19.8% vs 11.1%, respectively; $P = .0001$). Ziv-aflibercept also is being studied in other stages of colorectal cancer treatment.

H&O How effective was ramucirumab for treating colorectal cancer in clinical trials?

APV Ramucirumab was approved by the FDA in April 2015 in combination with FOLFIRI for patients with metastatic colorectal cancer that had progressed on bevacizumab, oxaliplatin, and a fluoropyrimidine. Approval was based on a double-blind multinational trial published by Dr Taberero and colleagues that enrolled 1072 patients who were randomly assigned to receive FOLFIRI plus ramucirumab or placebo every 2 weeks until disease progression or

unacceptable toxicity. Patients who received ramucirumab had a statistically significant improvement in progression-free survival compared with those who received placebo (HR, 0.79; 95% CI, 0.70-0.90; $P < .001$). The median progression-free survival was 5.7 months vs 4.5 months, respectively. Overall survival was also significantly increased for those receiving ramucirumab (HR, 0.85; 95% CI, 0.73-0.98; $P = .022$). The median overall survival was 13.3 months vs 11.7 months, respectively.

H&O Could you describe the clinical trial for regorafenib approval in colorectal cancer?

APV In 2012, regorafenib was approved by the FDA for patients with metastatic colorectal cancer who have previously received a fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy and an anti-VEGF therapy. Approval was based on a randomized double-blind study published by Dr Grothey and colleagues that randomly assigned 760 patients to receive chemotherapy with regorafenib or placebo. Patients receiving regorafenib had a significantly improved overall survival compared with those receiving placebo, with a median of 6.4 months vs 5.0 months (HR, 0.77; 95% CI, 0.64-0.94; $P = .0052$). Progression-free survival was also longer in patients receiving regorafenib (HR, 0.49; 95% CI, 0.42-0.58; $P < .0001$). The median progression-free survival was 2 months (95% CI, 1.9-2.3) vs 1.7 months (95% CI, 1.7-1.8), respectively. Partial responses were observed in 5 patients in the regorafenib group (1%) and 1 patient in the placebo group (0.4%). No differences in overall response rates were observed.

H&O Are any angiogenesis inhibitors being studied as single agents?

APV At least in colorectal cancer, none of these drugs appear to be effective by themselves, with the exception of regorafenib.

H&O At what stages of treatment are these inhibitors are being used?

APV They initially are introduced later in disease progression. If they appear promising and have a good safety profile, they are then tested earlier in the disease.

H&O How effective are angiogenesis inhibitors in colorectal cancer?

APV It is clear from the previously mentioned clinical trial results that angiogenesis inhibitors are only modestly effective in colorectal cancer. Some malignancies

are extremely sensitive to angiogenesis inhibitors, but colorectal cancer is not. So at least right now, they are marginal players.

H&O What are the side effects of these angiogenesis inhibitors?

APV For this class of drugs, the main side effect is hypertension, with a risk of thrombosis, heart attack, or stroke. Other serious side effects include gastrointestinal perforation and hemorrhage. In general, major complications occur in approximately one in 25 patients.

H&O What is your opinion on the value of angiogenesis inhibitors in colorectal cancer?

APV In a straight value judgment on the quality-adjusted life years gained from bevacizumab, the drug is not particularly cost-effective. Some patients undoubtedly receive a huge benefit from these drugs, but on average, the benefit is much less. Our challenge would be to find a biomarker that could determine who responds best to angiogenesis inhibitors, but we have not been able to find one so far.

H&O Why are angiogenesis inhibitors generally less effective in colorectal cancer compared with other cancer?

APV In colorectal cancer, there are a lot of different treatments, and physicians mix and match them depending on the patient. The patients do much better if many treatments are used rather than just a few of them. This means that attributing benefit to a specific drug can become difficult. In colorectal cancer, I think physicians tend to “bob and weave.” We start with a treatment, move to another, and then go back to another. In the mix of these drug regimens, angiogenesis inhibitors are valuable. Some patients respond very well and get a lot of benefit from these drugs, but most patients get very little benefit on average.

H&O What do you think is the future of angiogenesis inhibitors in colorectal cancer?

APV I think that a very important goal right now is finding a biomarker. I have no doubt that there is a subset of patients who are very sensitive to angiogenesis inhibitors and get the most benefit from these drugs. Our task is to determine which patients those are. Instead of giving the drugs to 100 patients and helping 20 patients, we would prefer to give the drugs to 20 patients and help all 20 patients.

Suggested Readings

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