

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Regorafenib in Metastatic Colorectal Cancer



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H&O What are the traditional palliative treatments in metastatic colorectal cancer?

AG Only a small subset of patients with metastatic colon cancer can be cured by liver resection, so most patients will require palliative chemotherapy. Treatment so far has relied on a combination of conventional chemotherapy agents and some biologics. The goal has been to expose patients to all potentially active agents, so that a sequential treatment approach can extend duration of survival. The treatment options include conventional chemotherapy with intravenous fluorouracil (5-FU); capecitabine (Xeloda, Genentech), an oral agent that is a substitute for 5-FU; oxaliplatin; and irinotecan. These agents are combined in regimens such as folinic acid, 5-FU, and oxaliplatin (FOLFOX); and folinic acid, 5-FU, and irinotecan (FOLFIRI), which are standard therapies in colorectal cancer. In the past 8 years, this regimen has been expanded to include the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab (Avastin, Genentech) and the epidermal growth factor receptor (EGFR) antibodies cetuximab (Erbix, Bristol-Myers Squibb/Lilly) and panitumumab (Vectibix, Amgen), which work only in patients who have *KRAS* wild-type tumors.

Although many patients still achieve a good performance status after 2 or 3 years of therapy, the tumors eventually progress on all available lines of therapies. These patients are in desperate need of the development of new, effective agents. Until recently, we did not have much to offer specifically for colorectal cancer. We have exposed patients to phase I trials and perhaps more unselected treatment options, such as liver-directed therapy, but we did not have a comprehensive approach or a particular drug for patients in this scenario.

H&O Could you please describe the novel agent regorafenib?

AG Regorafenib is a novel oral multikinase inhibitor of VEGF receptor 2 and tyrosine kinase, which play crucial roles in the biology of normal and tumor vasculature. It also inhibits additional angiogenic kinases (VEGF receptor 1/3, platelet-derived growth factor receptor-beta, and fibroblast growth factor receptor 1) and the mutant oncogenic kinases KIT, RET, and B-Raf. These pathways are considered important for tumor biology, such as those that lead to tumor cell proliferation, those that activate angiogenesis, and those that modify the tumor-host interaction. The idea of using a multitargeted inhibitor—meaning an inhibitor that is very promiscuous in its activity—is based on the fact that we know that 2–3 years of therapy can change the biologic profile of a tumor and activate a multitude of intracellular pathways. Therefore, a surgical, very specific treatment might not be the right approach in a patient who has undergone 2 or 3 years of therapy, during which the tumors have changed and have activated multiple different pathways. Regorafenib is an oral agent that is taken once a day. The tablets are 40 mg, and the standard dose is about 160 mg/day in a 3-week-on, 1-week-off schedule. Patients can usually tolerate this treatment reasonably well when dose modifications are made as soon as toxicities develop.

H&O What was the design of the phase III CORRECT trial?

AG The CORRECT (Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) trial included patients who experienced progressive

disease or intolerability on all available standard treatment options, including 5-FU/capecitabine, irinotecan, oxaliplatin, bevacizumab, and EGFR antibodies (in patients with *KRAS* wild-type tumors). These patients had a good performance status and had run out of treatment options. They were randomized to regorafenib or placebo in a 2:1 fashion. There were 760 patients randomized worldwide, with most patients in the United States, western Europe, and Japan. The primary endpoint of the trial was overall survival. Secondary endpoints included progression-free survival, response rate, duration of disease control, disease control rate—a combination of stable disease and response rate—and quality of life.

H&O What were the study results?

AG The primary endpoint was met; regorafenib improved overall survival in the entire study population. There was a 23% reduction in deaths (hazard ratio, .77) in the regorafenib arm. This decrease corresponded to a median improvement in overall survival from 5.0 months without regorafenib to 6.4 months with regorafenib. The *P* value was highly statistically significant, at 0.0052. An independent data safety monitoring committee closed the trial after a prespecified interim analysis suggested it would be unethical to withhold regorafenib from patients in the placebo group.

Secondary endpoints were improved, too. For progression-free survival, the hazard ratio was .49, meaning there was a 50% reduction of progression events in the study, which was highly statistically significant. The progression-free survival curve that we demonstrated also highlighted that only a subgroup of patients benefited from regorafenib. Future research will try to highlight and refine the patient population that can actually benefit from regorafenib, perhaps with the use of prespecified biomarkers. In this trial, regorafenib mainly stabilized tumors and did not induce tumor regression in a substantial number of patients, so the strength of the drug was in preventing tumors from growing.

H&O Was regorafenib associated with adverse events in this trial?

AG In the regorafenib arm, 17% of patients had hand-foot skin reactions, which were managed by dose delays and dose reduction. There was also some fatigue and mild diarrhea. Regorafenib is an active drug, with side effects that are similar to those seen with other oral agents, such as sunitinib (Sutent, Pfizer) and sorafenib (Nexavar, Onyx). In experienced hands, however, these adverse events should be manageable. In the CORRECT

trial, approximately 8% of patients stopped regorafenib due to drug-related adverse events, compared with 1% of patients who discontinued on placebo.

H&O What is next for regorafenib?

AG Regorafenib will undergo evaluation by the US Food and Drug Administration (FDA). In view of the survival benefit, it is hoped that regorafenib will be approved in the next year for the patient population that was tested in this trial: patients who have run out of conventional treatment options, who still have good performance status, and who are considered candidates for such an oral agent.

When regorafenib is available, it should be used as a single agent in a refractory patient population setting, meaning patients who cannot receive other drugs or who have received all other available agents and have experienced tumor progression. There are studies under way examining regorafenib in other settings, including in combination with chemotherapy and in earlier lines of therapy. At this point, evidence supports the use of regorafenib as a single agent in patients with treatment-refractory colorectal cancer.

H&O What are some areas of research in colorectal cancer?

AG The holy grail of clinical research in colorectal cancer is to have more individualized approaches or more targeted approaches to specific patient populations. For example, we are in the process of identifying molecular patterns and biomarker patterns in patients. A group that stands out in colorectal cancer is patients with *BRAF*-mutated colon cancers. These patients have a poor prognosis; their tumors are very aggressive, and they live half as long as patients without *BRAF* mutations. These patients would benefit from a targeted approach, and clinical research is under way to identify and develop treatment options for them. I believe that the era in which we unselectively randomize a large cohort of patients to a certain treatment is probably ending, as we learn more about specific biologic characteristics of colorectal cancer and other cancers.

Suggested Reading

Grothey A, Sobrero AF, Siena S, et al. Results of a phase III randomized, double-blind, placebo-controlled, multicenter trial (CORRECT) of regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients (pts) with metastatic colorectal cancer (mCRC) who have progressed after standard therapies. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Annual Meeting). 2012;30(suppl 4): Abstract LBA385.