CLINICAL UPDATE

Advances in the Treatment of Colorectal Cancer

Regorafenib in Metastatic Colorectal Cancer: Optimal Dosing and Patient Selection Recommendations

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In the United States, colorectal cancer is the third most common cancer and the second leading cause of death among cancers that occur in both sexes.[1] Approximately 40% of patients with colorectal cancer will develop metastatic disease,[2] and these patients represent an unmet need. Throughout the past 2 decades, overall survival has improved with the introduction of novel treatments, consisting mostly of chemotherapy agents but also targeted therapies.[3] Palliative therapy for metastatic colorectal cancer has improved outcomes not through one breakthrough that has changed the prognosis, but rather by incremental improvements associated with the introduction of different treatment regimens. Current management employs sequential therapies consisting of combinations of chemotherapy and antibodies, with targets such as the epidermal growth factor receptor (EGFR) and the angiogenesis vascular endothelial growth factor (VEGF) system. Regorafenib (Stivarga, Bayer HealthCare), a multikinase inhibitor, has improved survival in metastatic colorectal cancer when used as a single agent in the salvage therapy setting.[4] Regorafenib inhibits the serine/threonine and tyrosine kinases, which control components of tumor-based angiogenesis, as well as intratumoral cell pathways that are associated with the aggressiveness and pathophysiology of cancer cells. Regorafenib is a potent inhibitor of the VEGF receptor kinases, the type 2 platelet-derived growth factor receptor, BRAF, and other intracellular pathways involved in the proliferation of cancer cells. Regorafenib was approved by the US Food and Drug Administration in 2012 for the treatment of patients with metastatic colorectal cancer who have previously received fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy; and an anti-EGFR therapy (if the patient is *KRAS*

wild-type). Approval was based on the randomized phase 3 CORRECT (Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) trial, which compared regorafenib with placebo and best supportive care in patients who had previously received standard chemotherapies, including fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab (Avastin, Genentech), and, if they were *KRAS* exon 2 wild-type, cetuximab (Erbitux, ImClone/Bristol-Myers Squibb/Lilly) and panitumumab (Vectibix, Amgen).[4] The trial randomized 760 patients in a 2-to-1 fashion to regorafenib or placebo. The study met the primary endpoint, improvement in overall survival, with a difference of 1.4 months favoring regorafenib. The median overall survival was 6.4 months in the regorafenib group vs 5.0 months in the placebo group. The hazard ratio (HR) was 0.77, meaning a 23% reduction in death (95% CI, 0.64-0.94; 1-sided P=.0052; Figure 1). Regorafenib also significantly improved progression-free survival (HR, 0.49; 95% CI, 0.42-0.58; P<.0001). The median progression-free survival was 2.0 months with regorafenib (95% CI, 1.9-2.3) vs 1.7 months with placebo (95% CI, 1.7-1.8). Scans performed 8 weeks after treatment indicated that 50% to 55% of patients in the regorafenib arm had progressive events; therefore, the progression-free survival curve showed that approximately 45% to 50% of patients benefitted from regorafenib. The current challenge is to identify before treatment which patients have a higher chance of benefit from regorafenib.

Adverse Events and Dosing

Regorafenib is associated with toxicities that differ from those usually seen with chemotherapy agents and even
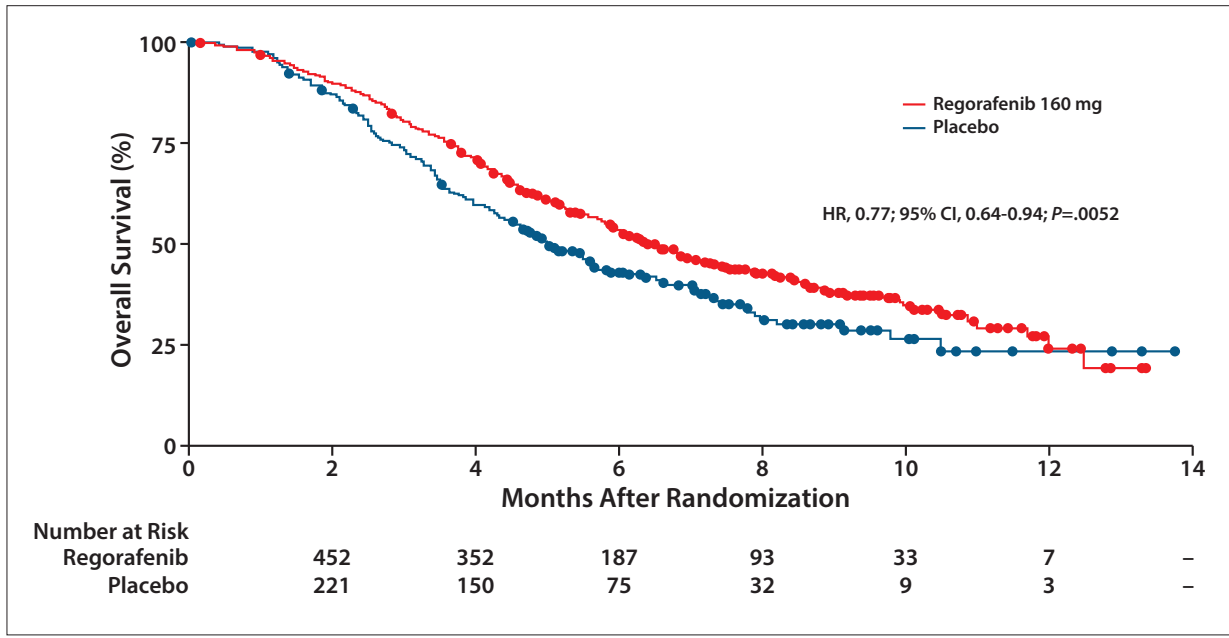
Figure 1. Median overall survival in the phase 3 CORRECT trial. CORRECT, Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy. Adapted from Grothey A et al. *Lancet.* 2013;381(9863):303-312.[4]
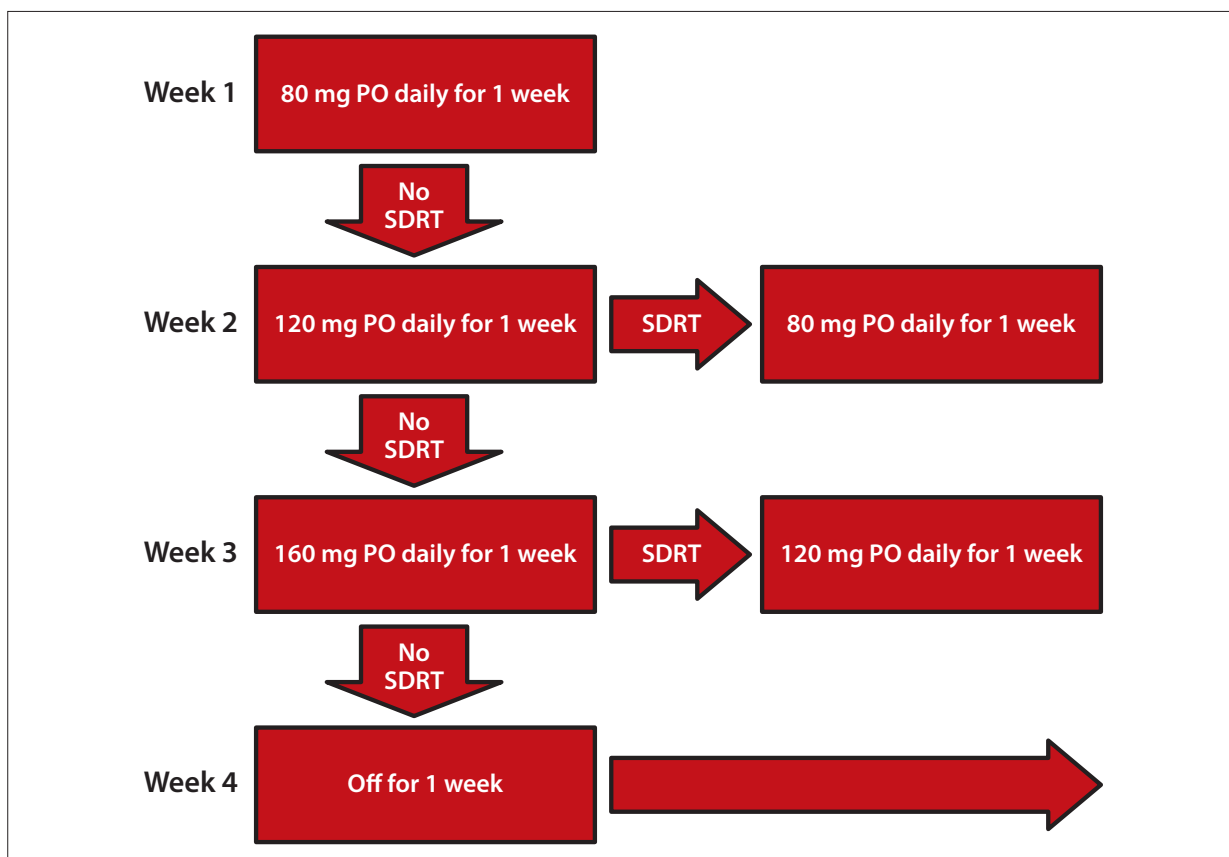

Figure 2. An incremental dose-escalation protocol for regorafenib to minimize toxicities in the first cycle of treatment. PO, by mouth; SDRT, significant drug-related toxicities.
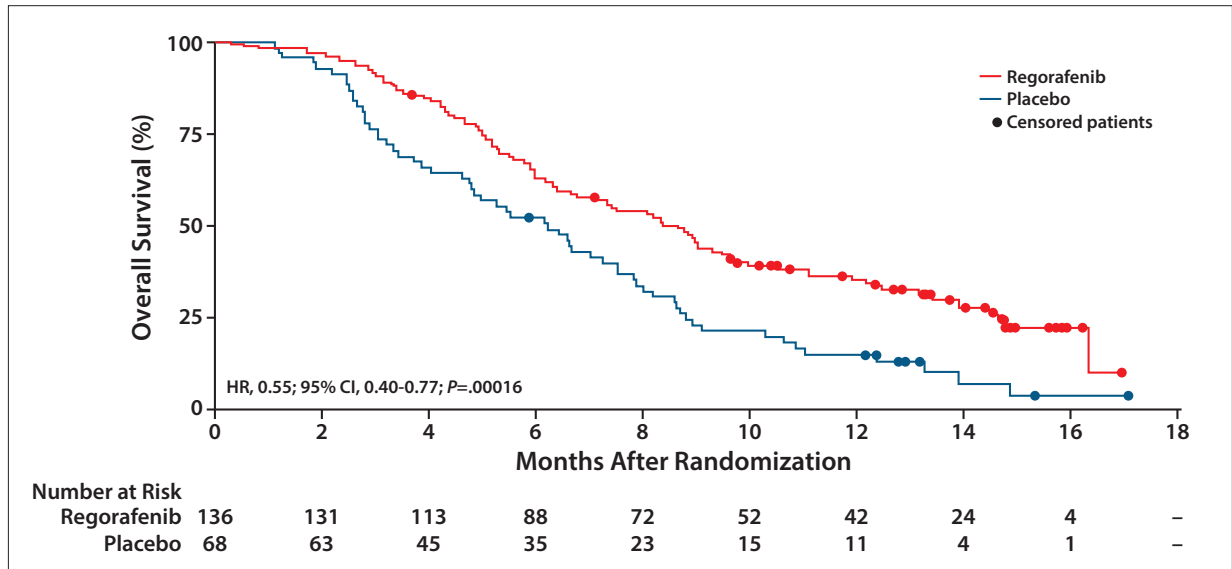
Figure 3. Median overall survival in the phase 3 CONCUR trial. CONCUR, Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy. Adapted from Li J et al. *Lancet Oncol.* 2015;16(6):619-629.[7]

other oral therapies. The primary adverse event is hand-foot skin reaction, which involves inflammation and blister formation adjacent to calluses, mainly on the feet.[4] Fatigue is another notable adverse event. These adverse events can occur early, within the first 3 weeks of regorafenib treatment, particularly in patients who receive the dosing strategy outlined in the package insert. This recommendation is 160 mg daily, which represents 4 pills taken at once in the morning after a light breakfast, for 3 weeks followed by 1 week off treatment. The flare-up of skin reactions, fatigue, and other adverse events during the initial treatment phase raises 2 important issues. First, it is necessary to monitor patients frequently. At the Mayo Clinic, patients who begin treatment with regorafenib return weekly for follow-up visits in the first treatment cycle. Second, these early toxicities challenge the idea that 160 mg is the right starting dose. They support a rationale of using incremental dose escalation protocols that start with a lower daily dosage, such as 120 mg or 80 mg. In my own clinical practice, I commonly start regorafenib at 80 mg daily for the first week, escalate the dosage to 120 mg daily for the second week, and then escalate the dosage to 160 mg daily, if possible, for the third week (Figure 2). A break is scheduled for the fourth week. In the second treatment cycle, dosing is based on how the patient responded in the first cycle. Quite commonly, the dosage used in the second cycle will be 120 mg daily, with some patients tolerating the higher dose of 160 mg.

The optimal dosing approach has yet to be resolved. Two trials of patients with metastatic colorectal cancer, one ongoing and one in the planning stage, are attempting to refine the dosing and schedule of regorafenib to make the treatment more tolerable for patients without losing efficacy.[5,6]

Patient Selection

There is no pretreatment biomarker that indicates which patients will or will not benefit from regorafenib. Regorafenib has a complex mechanism of action that might never allow identification of a single biomarker, or even a biomarker signature, that fits every patient. It may be that the efficacy of regorafenib in individual patients results more from the inhibition of an individual molecular signature rather than a link to one specific biomarker.

Currently, the most important selection criteria for regorafenib are the patient's clinical factors, in particular, performance status and extent of previous treatment. Clinical experience shows that patients who have a deteriorated performance status do not respond to regorafenib; in the worse-case scenario, these patients could experience side effects without any benefit.

The phase 3 CONCUR (Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) study, conducted in Asia, enrolled a less heavily pretreated patient population compared with the earlier CORRECT study.[7] Bearing in mind the caveat against comparing data across clinical trials, improvements in overall survival and progression-free survival were stronger in CONCUR than CORRECT. In the CONCUR trial, median overall survival was 8.8 months with regorafenib vs 6.3 months with placebo (HR, 0.55; 95% CI, 0.40-0.77; 1-sided P=.00016; Figure 3).[7] Median progression-free survival was 3.2 months with regorafenib vs 1.7 months with placebo (HR, 0.311; 95% CI, 0.222-0.435; 1-sided P<.0001). Data from CONCUR suggest that

regorafenib should be used before patients deteriorate and before the reuse of previous lines of chemotherapy. It is important to ensure that patients receive regorafenib when they still have a good performance status and are suitable candidates.

Conclusion

Regorafenib is an important tool that can improve survival in patients with metastatic colorectal cancer. Use of regorafenib requires a learning curve concerning patient selection, the dosing schedule, and the management of toxicities. Among patients who benefit, the response can be durable.

Disclosure
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