Regorafenib in previously treated metastatic colorectal cancer

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The multikinase inhibitor regorafenib was recently approved for the treatment of patients with metastatic colorectal cancer (mCRC) who had been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF therapy, and, for patients with wild-type *KRAS* tumors, anti-EGFR therapy.[1] Regorafenib inhibits numerous membrane-bound and intracellular kinases involved in normal cell function and in oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment (including RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-α, PDGFR-β, FGFR1, FGFR2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, $BRAF_{V600E}$, SAPK2, PTK5, and Abl kinases). The approval was based on findings in the international, phase 3 CORRECT trial.[2]

In CORRECT,[2] of 760 mCRC patients with progression during or within 3 months after their last standard chemotherapy or who had stopped standard therapy because of unacceptable toxicity 505 were randomized to receive regorafenib 160 mg orally once daily and 255 to receive placebo, both in addition to best supportive care. Treatment was given for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity. Patients had to be aged at least 18 years and have an ECOG performance status of 0 or 1. They had to have received as many of the following as were licensed in the country in which they received treatment: a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and, for those with wild-type *KRAS* tumors, cetuximab or panitumumab. The primary end point of the trial was overall survival (OS).

Patients in the regorafenib and placebo groups were generally well matched for median age (61 years in both groups), sex (62% and 60% men, respectively) race (78% and 79% white), region (North America, Western Europe, Israel, and Australia for 83% of both groups, and Asia for 14% of both groups), ECOG performance status (0 in 52% and 57%), primary site of disease (colon, 64% and 68%; rectum, 30% and 27%; both, 6% and 5%), presence of *BRAF* mutation (4% and 2%), histology (adenocarcinoma, 98% and 96%), number of previous systemic therapies given on or after diagnosis of metastatic disease (1 or 2 in 27% and 25%, ≥ 4 in 49% and 47%), and time from diagnosis of metastatic disease (≥ 18 months, 82% and 81%). All of the patients had received prior bevacizumab. A greater proportion of patients in the placebo group had a *KRAS* mutation (62% vs 54%). A greater proportion of placebo patients had progressed while receiving a fluoropyrimidine (87% vs 83%), bevacizumab (84% vs 80%), irinotecan (90% vs 80%), and oxaliplatin (63% vs 55%), with similar proportions progressing while receiving panitumumab or cetuximab (42% vs 43%).

The mean duration of treatment was 2.8 months (median, 1.7 months; interquartile range [IQR] 1.4-3.7

What's new, what's important

The oral multikinase inhibitor regorafenib for patients with metastatic colorectal cancer who have been heavily pretreated, acts by inhibiting membrane-bound and intracellular kinases involved in normal cell function and in oncogenesis, tumor angiogenesis, and maintaining the tumor microenvironment. The primary endpoint of the trial on which its approval was based was mean overall survival (6.4 months with regorafenib, 5.0 months with placebo). An encouraging finding on the face of it, but a number of points should be considered before prescribing the drug for this population: the benefits of the drug were modest and the toxicities substantial; no patients in the study had a complete response, and only 1% of them responded to the treatment; and although OS at 3 months was greater in the regorafenib group, there was no difference in OS between the 2 groups at 1 year. Moreover, most patients with metastatic disease are in their 70s and none of the trial participants was in that age range. And as always, we need to be mindful of the cost-benefit relationship when it comes to weighing patient well-being and quality of life. The recent Zaltrap developments are still fresh in our minds.

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How I treat metastatic colorectal cancer

Elderly patients present a number of difficulties to the clinician. These problems could include functional impairment, decreased functional reserve, the effects of polypharmacy, cognitive impairment, poor social support and others that may interfere with treatment decisions.

Based on clinical trial data, older patients derive the same benefit from therapies as do as younger patients, however, they have a different spectrum of toxicity and certain drugs may be more toxic in older patients particularly because of patient comorbidities. In terms of adjuvant treatment, older patients should be given the same treatment options as are younger patients. There is some controversy regarding the use of oxaliplatin in stage III disease, however, patients who have a good performance status with minimal to no functional impairment should be given the same therapy.

In terms of metastatic disease, again, clinical trial data indicates that older patients derive the same benefit as do younger patients. The same controversy prevails over the use of oxaliplatin, irinotecan, and bevacizumab. Findings reported in retrospective studies have shown that older patients might not derive the same degree of benefit with those drugs, but again, functional impairment and other geriatric-related complications should be taken into account when making this decision.

Most of the data derived from clinical trials come from studies in which older patients comprise a very small subset of the overall patient group. Clinical trial patients often are not representative of older patients, but they do provide a database for clinicians to draw on when they are making therapy decisions. However, there have been studies that are useful guides when making clinical decisions for older patients. An excellent example is a trial by the Cancer in Aging Research Group[1] in which a prospective evaluation in an older patient population has provided a risk stratification schema to predict the risk of chemotherapy-induced toxicities.

There are a number of other tools that can be used to screen elderly patients for health-related risks, such as the Vulnerable Elders Survey (VES-13) for identifying elderly individuals who are at risk for health deterioration, and monitoring activities of daily living (ADLs) and instrumental activities of daily living (IADLs), patient gait, history of falls, social support, geriatric syndromes, or some assessment of cognitive impairment. Older patients should be given the same opportunities as younger patients receive to benefit from chemotherapy. Clinical decision making should not be made on the basis of patient age alone, and clinicians should encourage older patients to participate in clinical trials.

Reference

1. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol*. 2011:29;3457-3465.

— Stuart M. Lichtman, MD

months) in the regorafenib group and 1.8 months (median, 1.6; IQR 1.3-1.7 months) in the placebo group. At the second preplanned interim analysis, regorafenib treatment was associated with a significant 23% reduction in risk for death (hazard ratio, 0.77; $P = .0052$). Median OS was 6.4 months (IQR, 3.6-11.8 months) in the regorafenib group and 5.0 months (IQR, 2.8-10.4 months) in the placebo group; OS at 3 months was 80.3% and 72.7%, respectively; at 6 months, 52.5% and 43.5%; at 9 months, 38.2% and 30.8%; and at 1 year, 24.3% and 24.0%. Regorafenib was associated with apparent OS benefit in all of the subgroups that were examined, except among patients with both colon and rectum as the primary site of disease (HR, 1.09 [95% CI, 0.44-2.70]). The magnitude of benefit was significant among patients with the colon as the primary site (HR, 0.70 [95% CI, 0.56-0.89]) but not among those with the rectum as the primary site (HR, 0.95 [95% CI, 0.63-1.44]).

Regorafenib was associated with significantly better progression-free survival (PFS; HR, 0.49, $P < .0001$); median PFS was 1.9 months (IQR, 1.6-3.9 months) in the regorafenib group, compared with 1.6 months (IQR, 1.4-1.9 months) in the placebo group. The PFS benefit was significant among patients with the colon as the primary disease site (HR, 0.55 [95% CI, 0.45]), those with the rectum as the primary site (HR, 0.45 [95% CI, 0.33-0.62]), and those with both as the primary site (HR, 0.35 [95% CI, 0.16-0.75]). No complete responses were observed. Objective response rates were 1.0% and 0.4%, respectively. Disease control rates were 41%, compared with 15% ($P < .0001$) and the median duration of stable disease was 2.0, compared with 1.7 months.

The most frequent adverse events of any grade in the regorafenib and placebo patients were fatigue (47% vs 28%, respecitvely), hand-foot skin reaction (47% vs 8%), diarrhea (34% vs 8%), and anorexia (30% vs 15%).

Adverse events of grade 3 or 4 occurred in 54% of regorafenib patients and in 14% of placebo patients; the most common in regorafenib patients were hand-foot skin reaction (17% vs < 1%), fatigue (10% vs < 1%), diarrhea (7% vs 1%), hypertension (7% vs 1%), and rash/desquamation (6% vs 0%). Serious adverse events occurred in 44% of regorafenib patients and in 40% of placebo patients, and dose modification due to adverse events occurred in 67% and 23%, respectively. Increases in liver transaminases and bilirubin were more common with regorafenib treatment, largely reflecting a greater frequency of grade 1 and 2 adverse events; 1 case of fatal regorafenib-related liver toxicity was observed. Thromboembolism occurred in 2% of patients in each group. Most of the 110 deaths that occurred during the study (58 in regorafenib patients and 35 in the placebo group) were due to disease progression. Death was attributed to adverse events in 8 regorafenib patients (2%; pneumonia and gastrointestinal bleeding in 2 each and intestinal obstruction, pulmonary hemorrhage, seizure, and sudden death in 1 each) and in 3 placebo patients (1%; pneumonia in 2 and sudden death in 1).

Health-related quality of life (QOL) was examined using the EORTC general health status and QOL questionnaire QLQ-C30 (range, 0-100; 0 = poorest, 100 = best QOL; change ≥ 10 points clinically meaningful) and health utility values were examined using the EuroQol 5-dimension index (EQ-5D; higher score = better; change of 0.06-0.12 points clinically meaningful) and visual analogue scale (change of 7-12 points clinically meaningful). Mean QLQ-C30 scores decreased from 62.6 at baseline to 48.9 at end of treatment in the regorafenib group and from 64.7 to 51.9 in the placebo group. Mean EQ-5D index scores decreased from 0.73 to 0.59 in the regorafenib group and from 0.74 to 0.59 in the placebo group; mean EQ-5D visual analogue scores decreased from 65.4 to 55.5 in the regorafenib group and from 65.8 to 57.3 in the placebo group.

Regorafenib has a boxed warning for severe and fatal hepatotoxicity and warnings and precautions for hemorrhage, dermatologic toxicity, hypertension, cardiac ischemia or infarction, reversible posterior leukoencephalopathy syndrome, gastrointestinal perforation or fistulae, wound healing complications, and embryofetal toxicity.[1] It is recommended that regorafenib be taken with a low-fat breakfast.

References

1. STIVARGA® (regorafenib) tablets prescribing information. Bayer HealthCare Pharmaceuticals Inc, September 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203085lbl.pdf.

2. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): and international, multicentre, randomized, placebo-controlled, phase 3 trial. Lancet 2012;http://dx.doi.org/10.1016/S0140-6736(12)61900-X.