Review Article

Meeting An Unmet Need in Metastatic Colorectal Carcinoma with Regorafenib

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Received: December 12, 2015, Accepted: December 25, 2015

ABSTRACT

Colorectal cancer is a global issue, affecting men and women equally. Over the last 25 years, advances in therapy and multidisciplinary care have led to improvements in survival for those with colorectal cancer. Despite these advances, more therapeutic options are needed for those being treated for this disease.Regorafenib is an oral drug that is a new therapeutic option for our patients. The CORRECT and CONCUR trials demonstrate the efficacy of regorafenib in the last line setting. This article summarizes some of the regorafenib clinical trial data and discusses the strategies to help manage the side effects of this drug including patient education, dose reductions and interruptions, and monitoring hypertension and liver function.

Key words: Metastatic colorectal cancer, oral therapy, overall survival, progression-free survival, regorafenib, side effect management

Introduction

Colorectal cancer affects people worldwide. Globally, 1.2 million new cases of colorectal cancerare diagnosed and approximately 693,900 people die of the disease each year.[1] The disease affects both men and women equally, and is the third most common cancer in men and the second most common in women.[1] Signs and symptoms of colorectal cancer include changes in bowel habits or bowel obstruction, intestinal bleeding/blood in stool, general abdominal discomfort, iron deficiency anemia, weight loss, and decreased appetite.[2] In half of the patients who are diagnosed with colorectal cancer, the disease will metastasize to another site, primarily to the liver, lungs, and lymph nodes.[3]

Drastic survival improvements over the last 25 years

Over the last 25 years, overall survival, defined as the time from official diagnosis of the disease to death, has

Access this article online	
Quick Response Code:	**Website:** www.apjon.org
	DOI: 10.4103/2347-5625.178174

Cite this article as: Melosky B. Meeting An Unmet Need in Metastatic Colorectal Carcinoma with Regorafenib. Asia Pac J Oncol Nurs 2016;3:58-65.

dramatically improved for colorectal cancer. In 1992, the *Journal of Clinical Oncology* reported that overall survival for colorectal cancer was just over 9 months for metastatic colorectal cancer (mCRC) patients treated with the available agents, 5-fluorouracilplus leucovorin.[4] In 2015, overall survival for mCRC patients with a *KRAS* wild-type status was over 30 months.[5]

Reasons for these dramatic improvements in survival for mCRC patientsinclude new systemic therapies, novel combinations of therapies, multidisciplinary team approaches, improvements in side effect management and better supportive care. Despite this good news, it isimportant to find more effective treatments. Our patients are often finishing all available lines of therapy, are still well and are requesting further treatments for their disease.

Current treatment options

Treatment goals for patients with mCRC include prolongation of survival, improvement of tumor-related symptoms, arresting tumor progression (disease control) and/or maintaining quality of life.[5] While systemic treatment options for mCRC have increased in the last 20 years, treatment paradigms are still limited. The standard of care differsfrom one jurisdiction to the next and is dependent on regulatory approval and availability. Generally, all mCRC patients are eligible for two lines of therapy.

Chemotherapy options

Current approved therapy options include chemotherapy and monoclonal antibodies against the vascular endothelial growth factor (VEGF)or the epidermal growth factor receptor (EGFR). Chemotherapy regimens include different combinations of systemic agents including leucovorin (also known as folinic acid or FOL), fluorouracil (F), irinotecan (IRI), oxaliplatin (OX)or capecitabine. The first line therapy regimen for fit patients is usually a combination of agentscalled FOLFIRI (leucovorin + fluorouracil + IRI) or FOLFOX (leucovorin + fluorouracil + OX). The second line therapy regimen usually includes agentsthat were not used in the first line. Some countries have approved a combination called FOLFIRINOX (leucovorin + fluorouracil + IRI + OX). This treatment combination essentially combines multiple lines of therapy into one.

Although different countries vary in their lines of therapy, multiple trials have demonstrated that patients who receive the most chemotherapy agents survive the longest.[6]

Monoclonal antibodies against vascular endothelial growth factor and epidermal growth factor receptor

mCRC patients who have *RAS* wild-type status ("wild-type" means that patients have no identified mutations in either *KRAS* or *NRAS* genes) are eligible for an additional line of therapy. Monoclonal antibodies directed against VEGF include bevacizumab and aflibercept, and monoclonal antibodies against EGFR include cetuximab and panitumumab. These monoclonal antibodies bind to their target andinhibit downstream signaling pathways. These monoclonal antibodies are often used in combinations with chemotherapy in the first, second, or third line setting. EGFR-directedmonoclonal antibodies are also used as solo agents in the third line setting.Patients who have *RAS* wild-type statusmay be offered panitumumab or cetuximab in the third line if they have notreceived them previously.

The world of RASmutations

In patients who have a *RAS* mutation, the RAS protein is constitutively activated and drives the signaling pathway downstream of EGFR. The original EGFR inhibitor trials were conducted in patients who were not selected on the basis of whether or not their tumors contained *RAS* mutations. Retrospective mutation analysis of these early trials has revealed that the EGFR inhibitors cetuximab or panitumumab are only efficacious in patients whose tumors did not harbor *KRAS* gene mutations.[7-11] Further studies have shown that*RAS* mutations emerge during anti-EGFR therapy.[12-14]

We originally estimated that up to 40% of our patients with mCRC had a *KRAS* mutation and thus were not eligible for cetuximab or panitumumab. This meant that more than 60% of patients were able to derive a possible benefit from anti-EGFR antibodies. Recently we discovered additional mutations in the *KRA*S and *NRAS* genes, which are detected in an additional 10-20% of mCRC patients. Not surprisingly, patients whose tumors have any of these mutations also do not respond to the anti-EGFR antibodies cetuximab and panitumumab. As a result of these additional mutations, the population of mCRC patients eligible for EGFR-inhibitors is diminishing. Now, less than 50% of mCRC patients are eligible for cetuximab or panitumumab, either alone or in combination as part of first, second, or third line of care [Figure 1].[15] As *RAS* mutation testing becomes more sensitive and more mutations are discovered, we anticipate that even fewer patients will be eligible for anti-EGFR treatment.

In addition to the shrinking number of patients who are candidates for EGFR-inhibitors, the new therapy

combinations condense multiple therapy lines into one. Until recently, options for patients who complete all available treatment options and still have a good performance status were limited andincluded best supportive care, participation in a clinical trial, or the use of any chemotherapy strategy not tried yet. There is a need for more options for fit mCRC patients who have exhausted all other lines of therapy.

Regorafenib: A Treatment Option for mCRC

Regorafenib is a relatively new multi-kinase inhibitorthat simultaneously affects a number of different pathways that are involved in cancer development and progression. This includesanti-angiogenic pathways including VEGFR1-3 and TIE2, stromal pathways such as platelet-derived growth factor receptor (PDGFR)-fibroblast growth factor receptor, and oncogenic drivers KIT, PDGFR, and RET. While the treatment goal of chemotherapy is to reduce tumor size, the goal of targeted therapies such as regorafenib is to stop or delay disease progression. Regorafenib has recently demonstrated efficacy in two randomized clinical trials, CORRECT and CONCUR.

The CORRECT and CONCUR trials

CORRECT and CONCUR trials were randomized, phase III trialconducted in mCRC patients who had failed all standard lines of therapy.[16,17] The study designs of the two trials were similar and are compared in Figure 2. CORRECT accrued very rapidly, in only 9 months, confirming anunmet need in patients who have progressed on all therapy. The CONCUR trial was conducted to confirm the regorafenib efficacy results from the CORRECT trial, but differed in that prior anti-VEGF or anti-EGFR targeted therapy was permitted, but not mandatory.[17]

Both trials met their primary endpoint of overall survival [Figure 3]. In the final updated analysis of the CORRECT trial, patients who were randomized to regorafenib had a median overall survival of 6.4 months (95% confidence interval [CI], 5.8-7.0) versus 5.0 months(95% CI, 4.4-5.9) for patients given a placebo (hazard ratio [HR] 0.79; 95% CI, 0.66-0.94; $P = 0.0038$).[16] In the CONCUR trial, patients randomized to regorafenib had a median overall survival of 8.8 months versus 6.3 months for patients given a placebo (HR 0.550, 95% CI 0.40-0.77, $P = 0.00016$).As illustrated in Figure 3, the overall survival curves from both trials split quickly and stayed apart, demonstrating the beneficial effect of regorafenib in this treatment-refractory population.

A secondary endpoint of both trials was progression-free survival, defined as the time from date of randomization to date of progression or death (whatever occurs earlier). This secondary endpoint was also met in both trials. The curve split at when the first computed tomography scan was done, at the 50-day mark [Figure 4]. In the CORRECT trial, the progression-free survival of patients on regorafenib was 1.9 months as compared to 1.7 months for patients who were on placebo (HR 0.49, 95% CI, 0.42-0.58, $P > 0.0001$).[16] The progression-free survival of patients on regorafenib in the CONCUR trial was 3.2 as compared to 1.7 months on placebo (HR 0.31, 95% CI 0.22-0.44, $P < 0.0001$). This amounted to a 69% reduction in risk of progression or death in the regorafenib group.[17]

Other secondary endpoints of these trials included objective response rates and disease control rates. Regorafenib not only significantly improved disease control rates compared with placebo, but the quality of life of patients on regorafenib in both trials did not deteriorate, but was

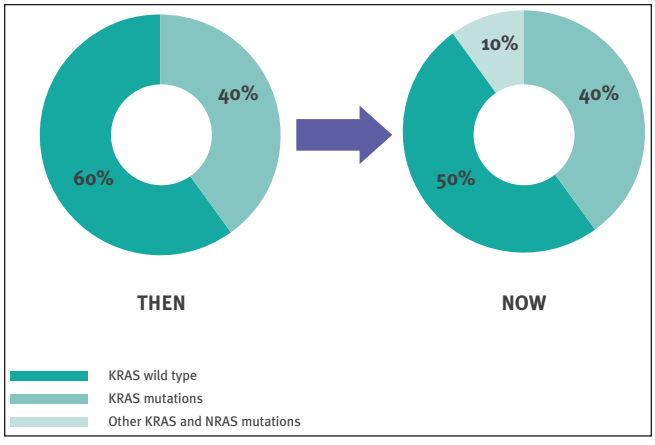

Figure 1: Distribution of RAS mutations in metastatic colorectal cancer then and now

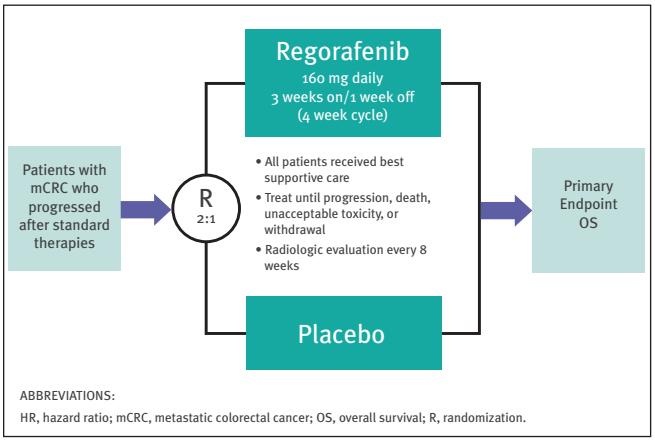

Figure 2: Study design for CORRECT and CONCUR trials

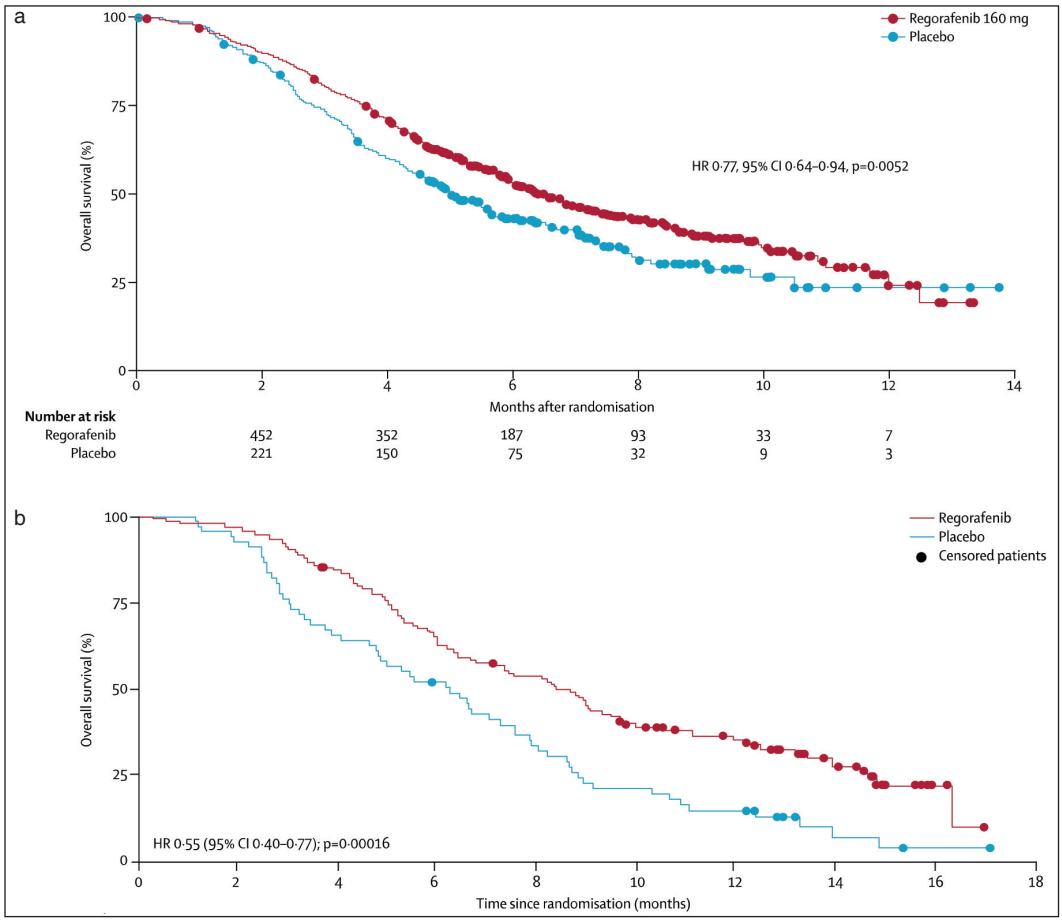

Figure 3: Overall survival curves of CORRECT and CONCUR. (a) Demonstrates the overall survival curve from the CORRECT trial. (b) Shows the overall survival curve from the CONCUR trial. Note: (a) Reprinted from The Lancet, Vol.381(9863), Grothey *et al.*, Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, phase 3 trial p. 303-12, copyright (2013), with permission from Elsevier. (b) Reprinted from Lancet Oncology, 16 (6), Li *et al.*, Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): A randomised, double-blind, placebo-controlled, phase 3 trial, p. 619-29, copyright (2015), with permission from Elsevier

equal to the quality of life of patients in the placebo arm. These results are impressive, especially in a group that is heavily pretreated and progressing.[16] Importantly, which patients benefitted most from regorafenib? A subgroup analysis of the CORRECT trial showed that almost all patient groups benefited from the regorafenib, regardless of gender, age, location (North America, Europe, Asia, and Australia), performance status or primary disease site (colon or rectum), whether their first diagnosis of metastatic disease to randomizationwas less or greater than 18 months or their prioranti-cancer treatment.The one exception was the group of patients with primary disease in both colon and rectum and was based on only a few events.[16]

In addition, the *KRAS* mutation status of all patients was analyzed, and was found to be neither prognostic nor predictive. Patients in both the *KRAS* wild-type and mutation subgroups experienced benefits in overall survival and progression-free survival. All patients, regardless of prior treatment or *RAS* status, can benefit from this treatment.[18]

Summary: Regorafenib efficacy

The CORRECT and CONCUR trials demonstrated that regorafenib is an important therapy for patients who have progressed after all standard therapy. An overall survival difference of 6.4 months for regorafenib compared with 5.0 months for placebo in CORRECT (and 8.8 vs. 6.3 months in CONCUR) is clinically meaningful, especially when there is no other standard treatment options exit for patients who have a good performance status and would like further treatment. The observed gain in survival was a median value; in clinical practice, many patients on regorafenib have prolonged survival. Regorafenib increased the overall survival in patients who are progressing with metastatic cancer after standard therapy. This should now become the new standard of care in this patient population.

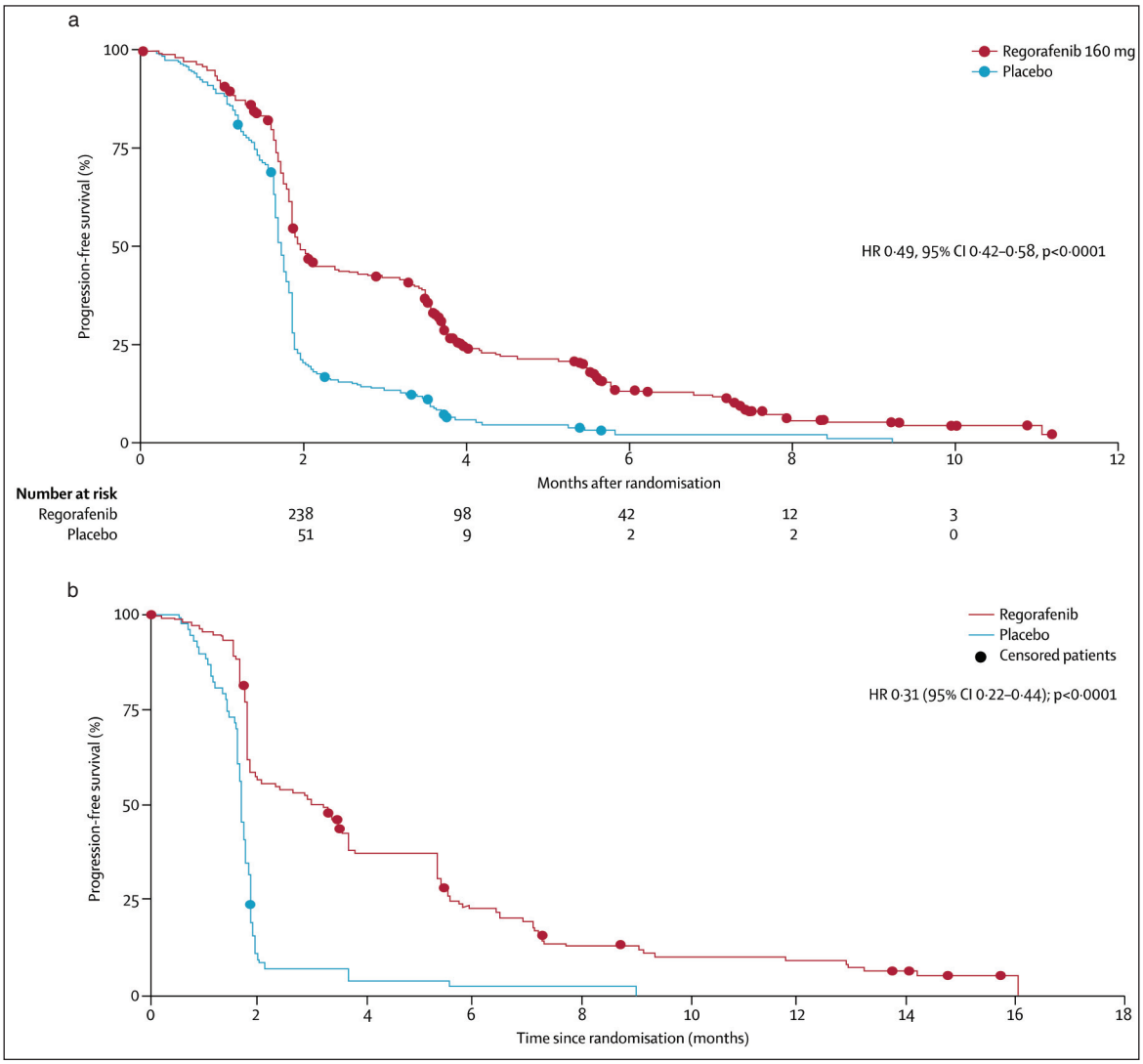

Figure 4: Progression-free survival curves of CORRECT and CONCUR. (a) Demonstrates the progression-free survival curve from the CORRECT trial. (b) Shows the progression-free survival curve from the CONCUR trial. Note: (a) Reprinted from The Lancet, Vol.381(9863), Grothey *et al.*, Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, phase 3 trial p. 303-12, copyright (2013), with permission from Elsevier.(b) Reprinted from Lancet Oncology, 16 (6), Li *et al.*, Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): Arandomised, double-blind, placebo-controlled, phase 3 trial, p. 619-29, copyright (2015), with permission from Elsevier

Patient Management Strategies for Regorafenib

In CORRECT, Grade 3 or 4 treatment-related adverse events occurred in 54% of patients randomized to regorafenib as compared to 14% of patients randomized to placebo.[16] The most common adverse events related to regorafenib compared to placebo in the CORRECT trial included hand–foot skin reaction (17% vs. <1%), fatigue (10% vs. 6%), diarrhea (8% vs. 1%), hypertension (7% vs. 1%) and rash/desquamation (6% vs. 0%).[16] Regorafenib-related side effects of the CONCUR trial included hand–foot skin reaction (16% vs. none), hypertension (11% vs. 3%), hyperbilirubinemia (7% vs. 1%), hypophosphatemia (7% vs. none), alanine aminotransferase (ALT) concentration increases (7% vs. none), aspartate aminotransferase (AST) concentration increases (6% vs. none).[17]

Patient education and management strategies

Patient education is an important feature of side effect management. We need to educate our patients about hand–foot syndrome and other adverse events and teach them to call the treating physician or nurse with any complications they may experience.

There are a number of supportive measures that care

providers can recommend to patients, includingcoaching patients to modify their activities of daily living [Table 1].

Table 1: Management strategies for hand–foot skin reactions

Management strategies for prevention and treatment of hand–foot skin reactions	
Aim	**Strategy**
Cushion and protect hands and feet	Avoid tight socks
	Wear well-padded footwear
	Use insole cushions or inserts in shoes
	Avoid walking long distances
	Prevent secondary infection by keeping hands and feet clean
	Avoid hot water
	Foot soaks with tepid water and Epsom salts
	Use a moisturizing cream after bathing
	Use socks/gloves to cover moisturizing cream
Control of calluses	Before initiating regorafenib treatment
	Check condition of hands and feet
	Have a manicure and pedicure prior to treatment
	Exfoliate rough spots with pumice stone
	During regorafenib treatment
	Avoid pressure points
	Avoid items that rub, pinch or create friction
Use of creams	General protection
	Early, continuous and liberal use of nonurea-based creams
	Examples: Cetaphil, aveeno, udderly smooth, gold bond, Norwegian formula, eucerin
	Hyperkeratotic lesion treatment
	Apply keratolytic creams (urea-based creams and salicylic acid 6%) sparingly and only to affected (hyperkeratotic) areas
	Gentle exfoliation
	Apply alpha hydroxy acids-based creams (5–8%) liberally 2 times each day
	Discomfort, pain, inflammation
	Topical corticosteroids (clobetasol 0.05%) or topical analgesics (lidocaine 2%), oral analgesics if needed

Table 2: Standard and reduced regorafenib dose levels

Dose level	Dose (mg/day)	Tablets
Level 0 (standard dose)	160	4
Level 1	120	3
Level 2	80	2

Patients should be advised to avoid tight socks, to wear well-padded footwear with insole cushions or inserts, and to avoid walking long distances. Patients should be advised to prevent secondary infection by keeping hands and feet clean, to avoid hot water, use tepid water and Epson salts for foot soaks. They should be advised to use moisturizing creams after bathing and use socks and gloves to protect hands covered in moisturizing cream. Patient should be taught how to control calluses before and during regorafenib treatment and should be advised about the use of creams to alleviate various symptoms.

Regorafenib dose reductions

Dose modifications are an important strategy for managing regorafenib-related side effects. Regorafenib is an oral tablet that comes in a 40-mg dose. Patients in the CORRECT trial were started on 160 mg, or four tablets/day. If necessary, this could be reduced to 120 mg (three tablets) or to 80 mg (two tablets)/day [Table 2].Treating physicians and nurses should not be afraid to modify or interrupt the dose of regorafenib to improve the side effect profile. Dose reduction strategies for regorafenib-related toxicities, hand-foots yndrome and hypertension are shown in Tables 3-5. Many patients will need a dose reduction and can continue on therapy without a detriment of their quality of life.

Monitoring blood pressure

As regorafenib can lead to hypertension, blood pressure should be monitored weekly for the first 6 weeks of treatment and reported to the treating physician if it is out of normal range (diastolic ≥100 mmHg and systolic ≥150 mmHg, or a ≥20 mmHg increase in diastolic measurement if the measurement was previously within normal limits).

Monitoring liver function

As regorafenib can affect liver function, we need to monitor liver enzymes. ALT, AST, and bilirubin are all important laboratory parameters to be ordered on a regular basis. A dose reduction or interruption may be necessary to manage liver-related side effects.

Table 3: Dose modifications for regorafenib-related toxicities except hand–foot skin reaction and hypertension[a]

NCI CTC version 3.0	Dose interruption	Dose modification	Dose for subsequent cycles
Grade 0-2	Treat on time	Level 0 (no change)	Level 0 (no change)
Grade 3	Delay until <Grade 2[b]	Level 1 (reduce by 1 dose level)	If toxicity remains < Grade 2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity (≥ Grade 3) recurs, institute permanent dose reduction
Grade 4	Delay until < Grade 2[b]	Level 1 (reduce by 1 dose level) Permanent discontinuation can be considered at treating investigator's discretion	

Table adapted from CORRECT protocol. [a]Excludes alopecia, nonrefractory nausea/vomiting, nonrefractory hypersensitivity and asymptomatic laboratory abnormalities, [b]If no recovery after a 4 week delay, treatment will be permanently discontinued. NCI: National Cancer Institute, CTI: Common Toxicity Criteria

Table 4: Dose modification for hand–foot skin reaction

Skin toxicity grade	Description	Occurrence	Suggested dose modification
Grade 1	Numbness, dysesthesia, paraesthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any	Maintain dose level and supportive measures
Grade 2	Painful erythema and swelling of the hands or feet and/or discomfort which affects the patient's normal activities	First occurrence	Consider 1 dose level reduction and supportive measures If no improvement - interrupt dose (7 days min) until resolves to Grade 0–1*
		No improvement ≤7 days or second occurrence	Interrupt dose until resolves to Grade 0–1 Resume at decreased dose level*
		Third occurrence	Interrupt dose until resolves to Grade 0–1 Resume at decreased dose by 1 additional level*
		Fourth occurrence	Discontinue therapy
Grade 3	Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	First occurrence	Supportive measures Interrupt dose (7 days min) until resolves to Grade 0–1 Resume at decreased dose by 1 additional level*
		Second occurrence	Supportive measures Interrupt dose (7 days min) until resolves to Grade 0-1 Resume at decreased dose by 1 additional level*
		Third occurrence	Discontinue therapy

Table adapted from CORRECT protocol. *If toxicity returned to Grade 0–1 after dose reduction. Dose re-escalation was permitted at the discretion of the investigator

Table 5: Management of regorafenib-emergent hypertension

Grade of event (CTCAE version 3.0)	Description	Management
Grade 1	—	Increase frequency of blood pressure monitoring
Grade 2	Asymptomatic Grade 2: Recurrent or persistent (= 24 h) increase by >20 mmHg (diastolic) or to >150/100	Begin anti-hypertensive therapy and continue regorafenib If diastolic BP is not controlled (≤100 mmHg) with the addition of new therapy, reduce one dose level[a]
	Symptomatic Grade 2: Any increase by >20 mmHg (diastolic) or to >150/100, associated with symptoms	Hold regorafenib until symptoms resolve and diastolic BP ≤100 mmHg[b]; also treat subject with anti-hypertensive medications If diastolic BP is not controlled (≤100 mmHg) with the addition of new therapy, reduce one dose level[a]
Grade 3		Hold regorafenib until symptoms resolve and diastolic BP ≤100 mmHg[b] and increase current anti-hypertensive medication(s)/add additional anti-hypertensive medications When regorafenib is restarted, reduce by one dose level[b] If diastolic BP is not controlled (≤100 mmHg) with the addition of more intensive therapy, reduce another dose level[c]
Grade 4	—	Discontinue therapy

Table adapted from CORRECT protocol. [a]BP remains controlled for at least one full cycle, dose re-escalation is permitted at the investigator's discretion, [b]Subjects requiring a delay of >4 weeks should go off therapy, [c]Subjects requiring >2 dose reductions should go off therapy. BP: Blood pressure, CTCAE: Common Terminology Criteria for Adverse Events

Conclusion

Patients with mCRC are now living longer than ever before. Treatment for mCRC continues to evolve. Fewer patients are eligible for EGFR inhibitors due to the discovery of *RAS* mutations.This has resulted in an unmet need for fitpatients who have exhausted all lines of therapy. Regorafenib is a therapy option in patients with mCRC in the end-of-line treatment setting. Despite adverse events experienced during treatment, patients treated with regorafenib can expect increased survival as well as a delayed time to deterioration in health status.[19]As an oral drug, side effects can be managed with patient education and coaching andproper dose reductions.

Acknowledgment

This article was originally presented as part of a lecture entitled "Efficacy of Regorafenib in the CORRECT and CONCUR Trials" at the International Conference on Cancer Nursing in July 2015 in Vancouver, Canada.

Financial support and sponsorship

Dr. Barbara Melosky was not compensated for writing this article. Chrystal Palaty, an independent communicator who was funded with an Educational Grant from Bayer Canada, provided project management and administrative support for this project. Bayer Canada did not participate in the preparation of this article.

Conflicts of interest

Dr. Barbara Melosky has received speaker honoraria from Boehringer Ingelheim, Eli Lilly, Pfizer, Roche, Merck,

Bristol-Myers Squibb, Novartis, Astra Zeneca. She has served as a consultant/advisory role with Boehringer Ingelheim and her institute has received research funding from Roche and Bayer.

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