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Symptom Management and Supportive Care

Optimizing Treatment Outcomes With Regorafenib: Personalized Dosing and Other Strategies to Support Patient Care

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Disclosures of potential conflicts of interest may be found at the end of this article.

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Abstract

Regorafenib is an oral multikinase inhibitor that inhibits several kinases relevant to tumor biology in several cancers, including colorectal carcinoma (CRC) and gastrointestinal stromal tumor (GIST). In phase III trials, regorafenib significantly improved overall survival versus placebo in patients with metastatic CRC progressing after all available standard therapies, and significantly prolonged progression-free survival in patients with advanced GIST in whom at least imatinib and sunitinib had failed. Thus, this agent holds promise as a new standard of care for CRC and GIST patients after disease progression following all other approved therapies. The clinical trials reported to date show that this new treatment has a consistent adverse event profile that is quite different from that of traditional cytotoxic chemotherapies. The most common adverse events of regorafenib include dermatologic and mucosal toxicities (especially hand-foot skin reaction, rash, and oral mucositis), constitutional symptoms (e.g., fatigue, nausea, and weight loss), vascular effects (especially hypertension), and gastrointestinal symptoms (e.g., diarrhea). To help health care professionals anticipate and manage the adverse events associated with regorafenib, we describe our experiences in clinical trials and show that such toxicities can be effectively managed with close observation of patients from initiation of dosing, along with prompt appropriate interventions, including dose modifications, if necessary. ***The Oncologist*** 2014;19:669–680

Implications for Practice: Regorafenib is a novel oral agent with documented efficacy in advanced colorectal cancer. It has a characteristic adverse event profile that consists of hand-foot skin reaction, fatigue, diarrhea, hypertension, and other less common events. This article details practical management strategies of these adverse events to optimize patient care and maximize the clinical benefit patients can derive from this novel agent.

Introduction

Regorafenib is an oral multikinase (serine-threonine and tyrosine-kinase) inhibitor that targets factors involved in angiogenesis (vascular endothelial growth factor [VEGFR] 1–3 and TIE2), oncogenesis (KIT, RET, RAF-1, and B-RAF), and regulation of the tumor microenvironment (platelet-derived growth factor receptor [PDGFR]-β and fibroblast growth factor receptors) [1]. In preclinical studies, regorafenib showed antitumor activity in a variety of tumor models, including models of colorectal carcinoma (CRC) and gastrointestinal stromal tumor (GIST) [1]. Regorafenib has been evaluated as a single agent in clinical trials in these two malignancies as well as other solid tumors (Table 1) [2–9].

Two recent pivotal phase III trials with regorafenib demonstrated positive clinical results. In the "CORRECT" trial involving 760 patients with metastatic CRC in whom all available standard therapies had failed (or who were unable to tolerate available treatments), median overall survival was significantly prolonged with regorafenib compared with placebo (6.4 months vs. 5.0 months, respectively; hazard ratio 0.77, 95% confidence interval 0.64–0.94; one-sided $p = .0052$) [7]. In the "GRID" trial involving 199 patients with advanced GIST that had progressed despite treatment with at least imatinib and sunitinib, median progression-free survival was 4.8 months with regorafenib compared with 0.9 months with placebo (hazard ratio 0.27, 95% confidence interval 0.19–0.39; $p < .0001$) [3]. These data confirm the role of regorafenib as an effective treatment option for patients with metastatic CRC or GIST in whom all standard therapies have failed.

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Similar to other oral therapies that target kinases relevant to cancer, regorafenib is associated with an adverse event profile that differs from that seen with traditional cytotoxic chemotherapy [10–12]. Health care professionals need to understand, recognize, and be able to manage these events so that patients have the best chance to benefit from this novel treatment. In this review, we highlight the adverse events that are most likely to occur with regorafenib and provide recommendations regarding their management.

Materials and Methods

To identify the most frequently reported adverse events associated with regorafenib treatment, we reviewed all of the presented and published safety and tolerability data on regorafenib reported in the clinical trials [2–9].

To identify relevant guidance on managing adverse events, we searched Medline (PubMed) using the search terms (kinase) AND (antagonist OR inhibitor) AND (safety OR toxicity OR tolerability OR adverse event) as well as abstracts from major oncology conferences (American Society of Clinical Oncology and the European Society for Medical Oncology annual meetings).

We have also drawn on our own databases and clinical experiences of using regorafenib in the clinical trials and after its regulatory approval in clinical practice to help inform the recommendations that we make in this article.

Regorafenib Adverse Event Profile

The study designs and patient characteristics for the regorafenib clinical trials are summarized in Table 1 [2–9]. Analysis of the most frequent drug-related adverse events reveals a consistent safety profile across all trials, regardless of patient population, ethnicity, previous treatment status, and tumor site or burden of disease (Table 2). The most common adverse events include dermatologic and mucosal toxicities (especially hand-foot skin reaction [HFSR], rash, and oral mucositis), constitutional symptoms (e.g., fatigue, nausea, and weight loss), systemic vascular effects (especially hypertension), and gastrointestinal symptoms (e.g., diarrhea).

More than half of the patients in each trial (range 49%–61%) experienced grade 3 or greater toxicities (based on National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 3.0 or 4.0) (Table 2) [2–9]. The most frequently reported grade 3 or higher events were HFSR (13%–33% of patients), hypertension (0%–36%), fatigue (0%–17%), diarrhea (3%–10%), and laboratory abnormalities, such as elevated aspartate or alanine aminotransferase (13% each, but reported in the Japanese trial only [5]), hypophosphatemia (4%–27%), or hyperbilirubinemia (2%–6%). The majority of grade 3 adverse events have appeared to be reversible with dose delays, dose reductions, and additional support [12]. It is important to note that side effects, in particular, HFSR, rash, and fatigue, occur early within the first cycle of therapy after a median of approximately 2 weeks [12]. To date, no clinical, biochemical, or molecular risk factors have been identified that predispose patients on regorafenib to the development of HFSR.

Mild asthenia and noticeable voice changes (most commonly hoarseness) are also frequent early features of regorafenib therapy and may occasionally occur with low-grade fever. Skin toxicities such as HFSR have also been observed with other oral therapies that target kinases including VEGFRs. In clinical trials, HFSR symptoms of any grade were reported in 34% of patients on sorafenib and 19% of patients on sunitinib; grade 3 or higher events affected 9% and 6% of patients, respectively [13, 14]. The mechanism of action of kinase inhibition responsible for HFSR remains to be elucidated, but it is believed to be a result of inhibition of multiple molecular pathways targeted by these agents, including VEGFRs, PDGFRs, and c-KIT [15, 16]. Of note, HFSR associated with kinase inhibitor therapy differs in important ways from the classic hand-foot syndrome seen with traditional cytotoxic agents such as 5-fluorouracil, capecitabine, doxorubicin, or liposomal doxorubicin (Table 3). Initial symptoms of HFSR mediated by kinase inhibitor therapies may manifest with early signs of tingling or subtle discomfort, even after only 5–7 days on therapy. These symptoms may progress in some patients to worsening pain, tenderness, callus formation, redness, and edema (occasionally associated with a burning sensation) in the palms of the hands or soles of the feet and especially in the folds between joints or pressure points of the feet. Other areas that may be involved include the tips of the fingers and toes, heels, and areas of flexure or overlying skin (Fig. 1). These pressure areas are where most severe symptoms are typically seen, with formation of blisters that can severely impair the ability to walk. These blisters can burst and discharge serous fluid, although, commonly, thick callus formation may occur. Signs and symptoms may appear concomitantly or sequentially, and can affect both hands and both feet [17, 18].

From our experiences in the phase III CRC and GIST trials, as well as earlier phase trials of regorafenib and in its use in clinical practice, we have noted that adverse events are likely to occur early—even during the first 3 days of regorafenib dosing—and the incidence of many adverse events is highest during the first cycle of treatment [12]. This time profile is similar to the timing of adverse events seen with other kinase inhibitors, such as sunitinib or sorafenib [19, 20].

Experience in the clinical trials indicates that most adverse events can be effectively managed with treatment breaks, dose adjustment, and appropriate intervention. By managing these events appropriately and proactively, particularly within the initial one or two cycles of therapy, most patients do not need to stop treatment permanently because of intolerable toxicities.

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It is important to note that to date no correlation has been established between the severity of specific adverse events such as hand-foot skin reaction and efficacy of regorafenib (data on file). This is in contrast to a report from a non-randomized population study in which the presence of skin

Table 1. Design, baseline patient characteristics, and efficacy outcomes of regorafenib clinical trials

Study	Phase	Design	Location	Cancer	Prior systemic therapy (lines)	Evaluable patients (*n*)	Age (yr)	ECOG	Regorafenib dose	Duration of treatment	Efficacy results
Mross et al. [8][a]	I	Nonrandomized, open-label	Germany (1 center)	Solid tumors	Median: 3 Range: 0–9	Efficacy: 47 Safety: 53	Median: 60 Range: 20–77	0: 49% 1: 47% 2: 4%	10 ($n = 3$) 30 ($n = 5$) 60 ($n = 6$) 120 ($n = 15$) 160 ($n = 12$) 220 ($n = 12$)	Median: 78 days Range: 3–1,239	DCR: 66% PR: 3/47 SD: 32/47
Strumberg et al. [9][a]	I	Nonrandomized, open-label	Germany (3 centers)	Colorectal cancer	Median: 4 Range: 0–7	Efficacy: 27 Safety: 38	Median: 64 Range: 36–85	0: 47% 1: 47% 2: 5%	60 ($n = 1$) 120 ($n = 4$) 160 ($n = 26$) 220 ($n = 7$)	Median: 53 days Range: 7–280	DCR: 74% PR: 1/27 SD: 19/27 Median PFS: 107 days
Furuse et al. [5]	I	Nonrandomized, open-label	Japan (4 centers)	Solid tumors	Median: 2 Range: 0–4	Efficacy: 15 Safety: 15	Median: 59 Range: 34–68	0: 80% 1: 20%	160	Median: 64 days Range: 28–603	DCR: 54% PR: 1/15 SD: 7/15
Bolondi et al. [2]	II	Nonrandomized, open-label	Europe, Asia (13 centers)	Hepatocellular carcinoma	Median: 1 Range: 1–4	Efficacy: 31 Safety: 36	Median: 61 Range: 40–76	0: 78% 1: 22%	160	Median: 15.5 weeks Range: 2–36	Median TTP: 4.1 months Median OS: not reached OS at 6 months: 80%
George et al. [6]	II	Nonrandomized, open-label	U.S. (4 centers)	Gastrointestinal stromal tumors	Median: 2 Range: 2–10	Efficacy: 33 Safety: 33	Median: 56 Range: 25–76	0: 70% 1: 30%	160	Median: 7 cycles Range: 2–17	DCR: 79% PR: 4/33 SD: 22/33 Median PFS: 10.0 months Median OS: not reached
Eisen et al. [4]	II	Nonrandomized, open-label	Europe, U.S. (18 centers)	Renal cell carcinoma	None	Efficacy: 48 Safety: 49	Median: 62 Range: 40–76	0: 61% 1: 39%	160	Median: 7.2 months Range: 1.7–34.8	DCR: 82% PR: 19/48 SD: 20/48 Median duration of response: 15.2 months Median PFS: 11.0 months Median OS: not reached
Grothey et al. [7]	III	Randomized, placebo-controlled	Worldwide (114 centers)	Colorectal cancer	Median: 4 Range: 1–12	Efficacy: 760 Safety: 753	Median: 61 Range: 22–85	0: 52.5% 1: 47.5%	160 ($n = 505$)	Median: 7.3 weeks Range: 0.3–47.0	Median OS: 6.4 months (HR 0.773 vs. placebo, $p = .0051$) PFS: 1.9 months (HR 0.493 vs. placebo, $p < .000001$) DCR: 45%
Demetri et al. [3]	III	Randomized, placebo-controlled	Worldwide (57 centers)	Gastrointestinal stromal tumors	2: 56.8% ≥3: 43.2%	Efficacy: 199 Safety: 198	Median: 60 Range: 18–87	0: 55.3% 1: 44.7%	160 ($n = 133$)	Median: 22.9 weeks Range: NS	Median PFS: 4.8 months (HR 0.27 vs. placebo, $p < .001$) Median OS: not reached DCR: 53%

In all trials, regorafenib (and matching placebo, where applicable) was given on days 1–21 of each 28-day cycle until disease progression, unacceptable toxicity, or patient/investigator decision to stop.

[a]The German phase I study included two parts: dose escalation and colorectal-cancer expansion; 15 patients with colorectal cancer were included in both analyses.

Abbreviations: DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NS, not specified; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to progression.

toxicity was associated with outcome parameters in patients with renal cell cancer treated with sunitinib [21].

Management of Regorafenib-Related Adverse Events

Our literature search identified 6,656 articles addressing the toxicity profile of kinase inhibitors and other targeted agents, 64 of which were focused on adverse event management (supplemental online Table 1). Understandably, given that experience with regorafenib to date has been mainly limited to clinical trials, no articles have yet been published that focus specifically on the practical management of regorafenib-related adverse events. The following information is therefore based on data and experience gleaned from the phase III clinical trials and the use of regorafenib in clinical practice, as well as our own and other groups' experience with other kinase inhibitors (in particular, multikinase inhibitors that inhibit VEGFRs, such as sunitinib and sorafenib).

Dose and Schedule Adjustments

As mentioned previously, the pertinent toxicities associated with regorafenib, in particular HFSR, may appear very early after initiation of therapy. Prompt management of these early events is critical to ensure tolerable treatment continuation. We advise evaluation of patients within 1 week of starting treatment and then at least every 2 weeks during the first 2 months (which corresponds to the first two treatment cycles)

to be able to address adverse events using dose delays or dose reductions. This evaluation would preferably be a face-to-face clinical assessment, but it could also be done by a telephone call conducted by a health care provider trained in regorafenib management. In the phase III clinical trials of regorafenib, only 8% of patients in the CRC study and 2% of patients in the GIST study permanently stopped regorafenib treatment because of adverse events unrelated to disease progression [8, 9]. Treatment modifications (dose reduction or delayed start of the next cycle) were used to manage adverse events in 56% of patients in the CRC study and 72% of patients in the GIST study [3, 7]. In some cases, patients were eventually able to return to the full dose of regorafenib once the toxicity had resolved to baseline levels without encountering recurrence of any severe adverse events. Table 4 shows the prespecified dose adjustments defined in the protocols of the phase III CRC and GIST trials.

For most patients, physicians were able to titrate regorafenib to an appropriately tolerable dose using the dose adjustment guidelines provided within the pivotal phase III studies [3, 7]. After initial dose delays and dose adjustments, patients tolerated long-term treatment with regorafenib with tolerable adverse events, with some patients now on regorafenib for more than 3 years, even if they had experienced severe (grade 3) toxicities within the first one or two cycles. Of note, the minimal daily dose of regorafenib allowed per protocol was 80 mg. This minimal daily dose was selected in view of the fact that no data on antitumor activity had been generated with lower doses in prior studies [9]. Experience with other kinase inhibitors also shows that dose and schedule modifications are important to minimize risk and reduce the frequency or severity of adverse events, thereby enabling patients to remain on treatment over time [18, 22, 23].

Supportive Care

There is little prospective research reported on appropriate supportive care interventions to manage adverse events associated with molecular targeted therapy. Much of the published advice exists in the form of expert opinion, consensus, or anecdotes (supplemental online Table 1). The advice provided in Table 4 and in the following text is similarly based on expert recommendations for other kinase inhibitors and our own experience managing patients during the course of regorafenib in clinical trials and clinical practice.

Dermatologic and Mucosal Toxicities

Although skin and mucosal toxicities are virtually never life-threatening, such symptoms can be painful, distressing, or even disabling. In our experience, HFSR, mucositis, and to a lesser extent rash, have a substantial impact on patients' quality of life [24]. Health care professionals therefore need to take proactive measures to prevent or minimize the impact of these symptoms.

Prevention

Patients should be educated about the potential risks of skin and mucosal toxicities, especially HFSR, and should have a full-body examination before the start of treatment to identify areas of pre-existing skin damage or hyperkeratosis/calluses, which should ideally be removed (e.g., by manicure or pedicure) before initiating regorafenib [15, 16, 25]. Pressure points should continue to be exfoliated with emollient or kerotolytic agent creams (e.g., salicylic acid 3%-, ammonium lactate/lactic acid 12%-, or urea 10%-based creams). Patients should be advised to wear cotton socks, avoid constrictive footwear, and prevent excessive friction or trauma to the hands and feet. In addition, patients should be advised to apply moisturizers and sunscreen, and avoid contact with hot water or chemicals (including household cleaners). Gloves should be worn if potentially skin-irritating chemicals are to be handled. Health care staff should frequently examine patients and encourage them to discuss any skin concerns to ensure early diagnosis of skin toxicities, particularly within the first 2 months of therapy.

Management

Table 5 shows the standardized NCI-CTCAE version 4.0 grading for dermatologic toxicities, which may be helpful in guiding treatment decisions [11, 17, 18, 25]. However, these criteria were not developed specifically for skin symptoms associated with targeted therapies. The Multinational Association of Supportive Care in Cancer (MASCC) Skin Toxicity Study Group has therefore proposed a modified grading scale tailored for epidermal growth factor receptor inhibitor therapy, which may also be relevant for VEGFR inhibitors [26]. Although the MASCC scale needs to be validated prospectively, this nonetheless may better enable physicians to detect and report skin toxicities with greater sensitivity, specificity, and range than is possible with previous scales or in conventional clinical practice.

At the first signs of redness, patients should be advised to moisturize the area with topical creams (e.g., zinc oxide and magnesium silicate lenitive cream without petrolatum), and preventive measures should be discussed again with the patient and caregivers. If blisters form, pressure should be avoided, and good supportive care to skin integrity should be pursued. Sometimes blisters have to be opened and drained under sterile conditions. Antibiotics should be prescribed only if there is evidence of infection. To prevent the risk of superinfection if fissures form, patients may be advised to soak their hands for 10 minutes every morning and evening in a solution of vinegar and water (equal measures). To reduce pain associated with walking, proper shoe fit is important, and podiatrist evaluation and support may be worth considering. A recent study has indicated that urea-based creams may provide prophylaxis for HFSR [27], but these creams should not be used if the patient develops broken skin, as such topical application may further irritate the skin.

If severe symptoms develop, patients should be offered pain relief and appropriate management to reduce the risk of infection. The regorafenib dose should be held until symptoms resolve and subsequently should be decreased (Table 4) to manage the toxicity and reduce the risk of treatment discontinuation.

Changes in Liver Enzymes and Bilirubin

Asymptomatic laboratory abnormalities (e.g., circulating levels of liver enzymes or bilirubin) have been relatively common in clinical trials of regorafenib. However, few patients experienced clinically significant abnormalities, although one death in each of the phase III trials was attributed to liver dysfunction, usually in the setting of concurrent metastatic

Table 2. Drug-related adverse events reported in regorafenib clinical trials

Adverse event	Grade	Mross et al. [8][a] ($n = 53$)	Strumberg et al. [9][a] ($n = 338$)	Furuse et al. [5] ($n = 15$)	Bolondi et al. [2] ($n = 36$)	George et al. [6] ($n = 33$)	Eisen et al. [4] ($n = 49$)	Grothey et al. [7] ($n = 500$)[b]	Demetri et al. [3] ($n = 133$)[b]	Range[c]
Any event	All grades	83	84	100	97	NR	NR	93	99	83–100
	Grade ≥3	49	58	NR	56	NR	NR	54	61	49–61
Voice changes	All grades	55	34	33	25	NR	35	29	11	25–55
	Grade ≥3	2	3	0	0	NR	0	<1	0	0–3
Hand-foot skin reaction	All grades	40	61	67	50	85	71	47	56	40–85
	Grade ≥3	19	32	13	14	24	33	17	20	13–33
Oral mucositis	All grades	36	18	NR	11	38	43	27	38	11–43
	Grade ≥3	2	0	NR	3	0	2	3	2	0–3
Diarrhea	All grades	32	24	67	50	61	45	34	41	24–67
	Grade ≥3	8	3	7	6	6	10	7	8	3–10
Hypertension	All grades	30	18	33	31	67	49	28	49	18–67
	Grade ≥3	11	11	0	3	36	6	7	24	0–36
Fatigue	All grades	28	50	33	47	79	53	47	39	28–79
	Grade ≥3	4	11	0	17	6	8	10	2	0–17
Anorexia	All grades	26	24	33	33	39	29	30	21	24–39
	Grade ≥3	2	0	0	0	0	6	3	0	0–6
Rash, desquamation	All grades	23	29	27	NR	NR	39	25	18	23–39
	Grade ≥3	6	5	0	NR	9	6	6	2	0–9
Alopecia	All grades	21	11	40	NR	28	45	7	24	7–45
	Grade ≥3	0	0	0	NR	0	0	0	2	0–2
Dry skin	All grades	NR	18	NR	NR	NR	NR	8	NR	8–18
	Grade ≥3	NR	0	NR	NR	NR	NR	0	NR	0
Muscle pain	All grades	NR	18	NR	NR	NR	NR	5	NR	5–18
	Grade ≥3	NR	0	NR	NR	NR	NR	<1	NR	0–<1
Dry mouth	All grades	NR	16	NR	NR	NR	NR	NR	NR	16
	Grade ≥3	NR	3	NR	NR	NR	NR	NR	NR	3
Weight loss	All grades	NR	13	40	14	NR	NR	14	NR	13–40
	Grade ≥3	NR	0	0	0	NR	NR	0	NR	0
Auditory disturbance	All grades	NR	11	NR	NR	NR	NR	NR	NR	11
	Grade ≥3	NR	0	NR	NR	NR	NR	NR	NR	0
Thrombocytopenia	All grades	NR	11	27	NR	NR	NR	NR	NR	11–27
	Grade ≥3	NR	3	0	NR	NR	NR	NR	NR	0–3
Hypophosphatemia	All grades	NR	NR	53	6	40	NR	5	NR	5–53
	Grade ≥3	NR	NR	27	6	15	NR	4	NR	4–27
AST elevation	All grades	NR	NR	53	NR	NR	NR	NR	NR	53
	Grade ≥3	NR	NR	13	NR	NR	NR	NR	NR	13
ALT elevation	All grades	NR	NR	47	NR	NR	NR	NR	NR	47
	Grade ≥3	NR	NR	13	NR	NR	NR	NR	NR	13
Proteinuria	All grades	NR	NR	47	11	NR	NR	7	NR	7–47
	Grade ≥3	NR	NR	7	3	NR	NR	1	NR	1–7
Hypoalbuminemia	All grades	NR	NR	47	NR	NR	NR	NR	NR	47
	Grade ≥3	NR	NR	0	NR	NR	NR	NR	NR	0
LDH elevation	All grades	NR	NR	47	NR	NR	NR	NR	NR	47
	Grade ≥3	NR	NR	0	NR	NR	NR	NR	NR	0
Constipation	All grades	NR	NR	33	22	NR	24	8	15	8–33
	Grade ≥3	NR	NR	0	0	NR	0	0	1	0–1
ALP elevation	All grades	NR	NR	33	NR	NR	NR	NR	NR	33
	Grade ≥3	NR	NR	0	NR	NR	NR	NR	NR	0

(continued)

Table 2. (continued)

Adverse event	Grade	Mross et al. [8][a] ($n = 53$)	Strumberg et al. [9][a] ($n = 338$)	Furuse et al. [5] ($n = 15$)	Bolondi et al. [2] ($n = 36$)	George et al. [6] ($n = 33$)	Eisen et al. [4] ($n = 49$)	Grothey et al. [7] ($n = 500$)[b]	Demetri et al. [3] ($n = 133$)[b]	Range[c]
Anemia	All grades	NR	NR	40	NR	NR	NR	NR	NR	40
	Grade ≥3	NR	NR	7	NR	NR	NR	NR	NR	7
Lymphopenia	All grades	NR	NR	33	NR	NR	NR	NR	NR	33
	Grade ≥3	NR	NR	27	NR	NR	NR	NR	NR	27
Leukopenia	All grades	NR	NR	27	NR	NR	NR	NR	NR	27
	Grade ≥3	NR	NR	7	NR	NR	NR	NR	NR	7
Hypothyroidism	All grades	NR	NR	NR	36	NR	NR	NR	NR	36
	Grade ≥3	NR	NR	NR	3	NR	NR	NR	NR	3
Nausea	All grades	NR	NR	NR	31	40	27	14	16	14–40
	Grade ≥3	NR	NR	NR	0	3	0	<1	1	0–3
Headache	All grades	NR	NR	NR	17	42	NR	5	NR	5–42
	Grade ≥3	NR	NR	NR	0	0	NR	1	NR	0–1
Vomiting	All grades	NR	NR	NR	14	NR	22	8	NR	8–22
	Grade ≥3	NR	NR	NR	0	NR	0	1	NR	0–1
Abdominal pain	All grades	NR	NR	NR	11	NR	NR	NR	NR	11
	Grade ≥3	NR	NR	NR	3	NR	NR	NR	NR	3
Hyperbilirubinemia	All grades	NR	NR	NR	8	NR	NR	9	NR	8–9
	Grade ≥3	NR	NR	NR	6	NR	NR	2	NR	2–6
Lipase increase	All grades	NR	NR	NR	NR	NR	8	NR	NR	8
	Grade ≥3	NR	NR	NR	NR	6	6	NR	NR	6
Hyperuricemia	All grades	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Grade ≥3	NR	NR	NR	NR	6	NR	NR	NR	6
Thromboembolic event	All grades	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Grade ≥3	NR	NR	NR	NR	3	NR	NR	NR	3
Myalgia	All grades	NR	NR	NR	NR	42	NR	NR	14	14–42
	Grade ≥3	NR	NR	NR	NR	3	NR	NR	1	1–3
Hoarseness	All grades	NR	NR	NR	NR	45	NR	NR	22	22–45
	Grade ≥3	NR	NR	NR	NR	3	NR	NR	0	0–3
Renal failure	All grades	NR	NR	NR	NR	NR	10	NR	NR	10
	Grade ≥3	NR	NR	NR	NR	NR	10	NR	NR	10
Hyponatremia	All grades	NR	NR	NR	NR	NR	8	NR	NR	8
	Grade ≥3	NR	NR	NR	NR	NR	6	NR	NR	6
Platelet abnormalities	All grades	NR	NR	NR	NR	NR	NR	12	NR	12
	Grade ≥3	NR	NR	NR	NR	NR	NR	3	NR	3
Fever	All grades	NR	NR	NR	NR	NR	NR	10	NR	10
	Grade ≥3	NR	NR	NR	NR	NR	NR	1	NR	1
Taste alteration	All grades	NR	NR	NR	NR	NR	NR	7	NR	7
	Grade ≥3	NR	NR	NR	NR	NR	NR	0	NR	0
Sensory neuropathy	All grades	NR	NR	NR	NR	NR	NR	7	NR	7
	Grade ≥3	NR	NR	NR	NR	NR	NR	<1	NR	<1
Hemoglobin abnormalities	All grades	NR	NR	NR	NR	NR	NR	7	NR	7
	Grade ≥3	NR	NR	NR	NR	NR	NR	3	NR	3
Nose bleed	All grades	NR	NR	NR	NR	NR	NR	7	NR	7
	Grade ≥3	NR	NR	NR	NR	NR	NR	0	NR	0
Dyspnea	All grades	NR	NR	NR	NR	NR	NR	6	NR	6
	Grade ≥3	NR	NR	NR	NR	NR	NR	<1	NR	<1

Data are percentages of patients.
[a]The German phase I study included two parts: dose escalation and colorectal cancer expansion; 15 patients with colorectal cancer were included in both analyses.
[b]Patients who received at least one dose of regorafenib during double-blind treatment.
[c]Range denotes lowest and highest incidence rates reported across the trials.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; NR, not reported.

Table 3. Clinical characteristics of hand-foot syndrome and hand-foot skin reaction

Characteristics	Hand-foot syndrome	Hand-foot skin reaction
Causal agents	Chemotherapeutics (fluoropyrimidines, esp. capecitabine, liposomal doxorubicin)	Multikinase inhibitors (e.g., regorafenib, sorafenib, sunitinib, axitinib, cabozantinib, pazopanib)
Manifestation	Hands > feet	Feet > hands
	Symmetrical, diffuse	More localized along pressure points
Time to onset	Weeks–months	Days–weeks
Key symptoms	Dysesthesia, erythema, scaling	Dysesthesia, erythema, scaling, pain, blisters at pressure zones

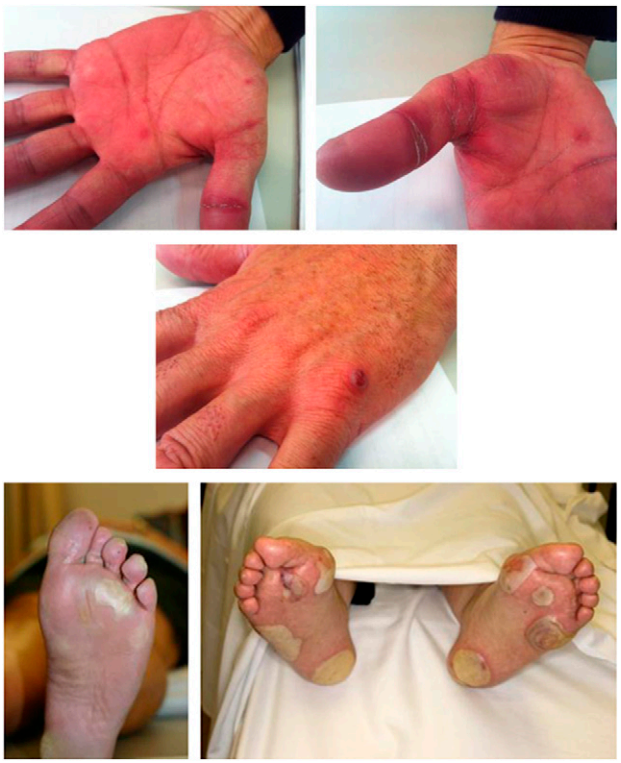

Figure 1. Clinical manifestations of hand-foot skin reaction.

disease burden affecting the liver [3, 7]. Because patients with advanced metastatic CRC and GIST commonly have liver metastases, the distinction between abnormalities in liver function due to tumor progression and regorafenib can be unclear. Until further evidence is available on the mechanism of regorafenib-induced liver dysfunction and the likely risk to patients in the general population, careful monitoring of liver function before and during treatment is recommended in the U.S. Federal Drug Administration-approved dosing information for regorafenib. Dose modifications or treatment discontinuation (Table 4) are mandated in the case of elevated liver function test results or hepatocellular necrosis, depending on severity and persistence (Table 6 shows the standardized NCI-CTCAE version 4.0 grading for liver function tests).

Systemic Vascular Toxicities and Potential Cardiovascular Risks

Hypertension was reported in 28% of patients in the phase III CRC trial and in 49% of patients in the phase III GIST trial at any grade, with 7% and 24%, respectively, experiencing grade 3 or higher hypertension [3, 7]. The higher rates of hypertension in the GIST trial could reflect the longer treatment duration compared with the CRC study (mean duration of treatment 20.2 weeks vs. 12.1 weeks, respectively), although this hypothesis has not been formally assessed. Abnormally elevated blood pressure may have an important impact on patients, who may experience clinical symptoms (e.g., headache) in the short term, or may have significant detrimental cardiovascular effects with longer term or severely uncontrolled hypertension. Therefore, the need for close and careful blood pressure monitoring and adjustment of medications should not be underestimated. Fortunately, with the introduction of VEGF inhibitors in the treatment algorithms of various cancers, blood pressure monitoring and management have become part of standard oncologic practice. Although hypertension is not a contraindication for regorafenib treatment, patients should have good control of any pre-existing hypertension, with normal baseline blood pressure. Patients should also be counseled and educated on antihypertensive treatment. Blood pressure should be monitored regularly while patients are taking regorafenib. In the GIST trial protocol, it was recommended that blood pressure should be monitored at least weekly for the first 6 weeks of treatment. In addition, we suggest further monitoring at least during the first week of subsequent cycles. Table 4 suggests that appropriate antihypertensive management and regorafenib dose adjustment be considered in patients with hypertension. The health care team needs to ensure that the patient has access to a blood pressure monitor at home, records blood pressure regularly in a log or diary, and is given instructions to contact the health care team for specified elevations in blood pressure. For example, we recommend that patients be instructed to contact the doctor's office if any single blood pressure reading is above 160/90 mmHg, and to review home blood pressures monthly, with a goal of keeping blood pressure below 140/90 mmHg. Patients should also be educated on the potential symptoms of hypertensive crisis and the appropriate actions to take.

Other cardiac and vascular toxicities have been reported with therapies that inhibit the VEGF signaling pathways, such as the monoclonal antibody bevacizumab [28, 29], and other targeted therapies have also been implicated in cardiac dysfunction [30]. Bleeding disorders or thromboembolic events have only rarely been reported in the regorafenib clinical trials and have not been of major relevance in clinical practice. Because of the potential impact of VEGF inhibition on cardiac and cardiovascular function, the clinical trials of regorafenib excluded patients with known pre-existing cardiovascular

Table 4. Recommended regorafenib dose modifications to manage adverse events (based on protocol-specified dose modifications in the phase III trials) [8, 9]

Adverse event	Grade	Occurrence	Dose modification	Other management
Hand-foot skin reaction	0	Prophylaxis	Consider urea 10%-based creams as prophylaxis	
	1	Any	None	Institute immediate supportive measures for symptomatic relief
	2	First	Consider decreasing study medication by one dose level If toxicity resolves to grade ≤1, dose re-escalation is permitted at the physician's discretion, up to a maximum of 160 mg/day If no improvement, interrupt study medication for ≥7 days, until toxicity resolves to grade ≤1	Consider topical corticosteroids (clobetasol, betamethasone) of high potency to mitigate painful areas on palms and soles and topical lidocaine (lidocaine 4% cream or lidoderm patches to painful areas)
		Second (or no improvement within 7 days of first)	Patients requiring interruption for 4 weeks must stop treatment permanently Interrupt study medication until toxicity resolves to grade ≤1 Patients requiring interruption for 4 weeks must stop treatment permanently When resuming study medication, reduce dose by one dose level If toxicity resolves to grade ≤1, dose re-escalation is permitted at the physician's discretion, up to a maximum of 160 mg/day	
		Third	Interrupt study medication until toxicity resolves to grade ≤1 Patients requiring interruption for 4 weeks must stop treatment permanently When resuming study medication, reduce dose by a further dose level If toxicity resolves to grade ≤1, dose re-escalation is permitted at the physician's discretion, up to a maximum of 160 mg/day Patients requiring more than two dose reductions must stop treatment permanently	
		Fourth	Discontinue study medication permanently	
	3	First	Interrupt study medication for ≥7 days until toxicity resolves to grade ≤1 Patients requiring interruption for 4 weeks must stop treatment permanently When resuming study medication, reduce dose by one dose level If toxicity resolves to grade ≤1, dose re-escalation is permitted at the physician's discretion, up to a maximum of 160 mg/day	
		Second	Interrupt study medication for ≥7 days until toxicity resolves to grade ≤1 Patients requiring interruption for 4 weeks must stop treatment permanently When resuming study medication, reduce dose by a further dose level If toxicity resolves to grade ≤1, dose re-escalation is permitted at the physician's discretion, up to a maximum of 160 mg/day Patients requiring more than two dose reductions must stop treatment permanently	
		Third	Discontinue study medication permanently	
Hypertension	1	Any	None	Consider increasing frequency of blood pressure monitoring
	2	Asymptomatic but recurrent or persistent ≥24 hours	If diastolic blood pressure is not controlled (to ≤100 mmHg) with the addition of antihypertensive therapy, reduce study medication by one dose level[a] If blood pressure remains controlled for at least one full cycle, dose re-escalation is permitted at the physician's discretion, up to a maximum of 160 mg/day	Institute antihypertensive therapy (long-acting calcium antagonists and ACE inhibitors preferred)
		Symptomatic	Interrupt study medication until symptoms resolve and diastolic blood pressure is <100 mmHg Patients requiring interruption for 4 weeks must stop treatment permanently If diastolic blood pressure is not controlled (to ≤100 mmHg) with the addition of antihypertensive therapy, reduce study medication by one dose level[a]	

(continued)

Table 4. (continued)

Adverse event	Grade	Occurrence	Dose modification	Other management
			If blood pressure remains controlled for at least one full cycle, dose re-escalation is permitted at the physician's discretion, up to a maximum of 160 mg/day	
	3	Any	Interrupt study medication until symptoms resolve and diastolic blood pressure is <100 mmHg Patients requiring interruption for 4 weeks must stop treatment permanently When resuming study medication, reduce dose by a further dose level[a] If blood pressure remains controlled for at least one full cycle, dose re-escalation is permitted at the physician's discretion, up to a maximum of 160 mg/day If diastolic blood pressure is not controlled (to ≤100 mmHg) with increased/additional antihypertensive therapy, reduce study medication by a further dose level[a] If blood pressure remains controlled for at least one full cycle, dose re-escalation is permitted at the physician's discretion, up to a maximum of 160 mg/day Patients requiring more than two dose reductions must stop treatment permanently	Increase or institute additional antihypertensive medication
Liver toxicities (ALT, AST, or bilirubin increases)	Increase from baseline grade 0 to grade 1, or baseline grade 1 to grade 2		None	Monitor liver function twice weekly for 2 weeks, then weekly for 4 weeks or until recovery to baseline
	Baseline grade 0 to grade 2		Interrupt treatment until grade ≤1 Patients requiring interruption for 4 weeks must stop treatment permanently When resuming study medication, reduce dose by one dose level[a] If values remain stable for two full cycles, dose re-escalation is permitted at the physician's discretion, up to a maximum of 160 mg/day If liver dysfunction recurs, discontinue study medication permanently	
	3		Interrupt treatment until toxicity returns to baseline Patients requiring interruption for 4 weeks must stop treatment permanently Reduce study medication by one dose level[a] If values remain stable for two full cycles, dose re-escalation is permitted at the physician's discretion, up to a maximum of 160 mg/day If liver dysfunction recurs, discontinue study medication permanently If ALT or AST >8 × upper limit of normal, with concomitant rise in bilirubin (of any degree) versus previous bilirubin values, consider permanent discontinuation at first occurrence	
	4		Discontinue study medication permanently	
Adverse events other than hand-foot skin reaction, hypertension, alopecia, nonrefractory nausea and vomiting, nonrefractory hypersensitivity, and asymptomatic laboratory abnormalities	1–2		None	
	3		Interrupt treatment until grade ≤1 Patients requiring interruption for 4 weeks must stop treatment permanently When resuming study medication, reduce dose by one dose level[a] If toxicity resolves to grade ≤1, dose re-escalation is permitted at the physician's discretion, up to a maximum of 160 mg/day If dose is re-escalated and grade ≥3 toxicity recurs, reduce dose permanently	
	4		Interrupt treatment until grade ≤1 Patients requiring interruption for 4 weeks must stop treatment permanently Reduce study medication by one dose level[a] Study medication may be stopped permanently at the physician's discretion	

[a]Regorafenib dose levels: 0 = 160 mg orally once daily (standard dose); −1 = 120 mg orally once daily; −2 = 80 mg orally once daily. The dose must not be reduced below 80 mg.
Abbreviations: ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase, AST, aspartate aminotransferase.

comorbidities, including arterial or venous thrombotic or embolic events such as stroke or transient ischemic attacks, deep vein thrombosis, or pulmonary embolism within the 6 months before the start of treatment, cardiac arrhythmias requiring antiarrhythmic therapy, or uncontrolled hypertension despite optimal medical management. Therefore, in the absence of data on the effect of regorafenib in these patients, we strongly advise caution when considering regorafenib treatment in such patients. Patients who were on stable anticoagulation treatment were allowed to participate in the trials, and excess bleeding was not seen. However, close monitoring of patients on Coumadin (warfarin) is recommended, or consideration should be given to using an alternative anticoagulant, such as a low-molecular-weight heparin.

Other Adverse Effects

Other frequent adverse events that may have a substantial impact on patients include fatigue, diarrhea, muscle aches, fever, hair thinning, and voice changes. Patients should be educated on these potential adverse events and the need to report any adverse events to the oncology team to allow appropriate and prompt intervention.

Fatigue can be significant and debilitating in the first few cycles, and symptoms, which are most prominent toward the end of dosing in each cycle, can begin early (e.g., hoarseness within the first 3–4 days) [12]. As many multikinase inhibitors have been noted to induce hypothyroidism, particularly after several months of therapy [31], we recommend checking thyroid-stimulating hormone (TSH) levels in patients with any level of fatigue (abnormally high TSH levels on regorafenib therapy are often clinically unapparent and not accompanied by changes in free triiodothyronine and thyroxine). If there is no laboratory evidence of hypothyroidism, the patient may be encouraged to exercise, which may help to mitigate mild fatigue. For grade 2 or 3 fatigue, regorafenib dose interruption or reduction should be considered. Indeed, decreased doses to 120 or even 80 mg/day may be necessary. There are no clinical data to support dosing regorafenib lower than 80 mg/day.

Diarrhea is generally a highly manageable adverse event with the use of standard antidiarrheal agents. Patients should be encouraged to keep a dietary log, which may identify the need for diet modification, including probiotics, lactose avoidance, and adequate hydration. If the patient experiences persistent grade 3 diarrhea despite antidiarrheal drugs and dietary modification, regorafenib dose interruption or reduction should be considered.

For other significant adverse events, regorafenib dose modifications (interruption or reduction) should be considered.

Discussion and Recommendations for Practical Management

Our experience in the phase III clinical trials, together with evidence from earlier phase trials and postapproval practice, indicates that regorafenib has a generally consistent and predictable profile of adverse events that can be managed with appropriate patient education, dose interruptions, dose modification, and supportive care. Adverse events are usually of a low grade, and events of grade 3 or higher are typically of short duration when identified promptly and managed optimally [12]. Due to their reversibility, adverse events can normally be managed without the need for permanent discontinuation of regorafenib treatment, and most patients are able to continue treatment until disease progression.

Close communication between the patient and the health care team allows prompt identification and management of toxicities to achieve adherence to regorafenib therapy. It is important to see or at least contact patients very soon after starting treatment (i.e., within the first week), and then see patients every 2 weeks during the first two cycles of regorafenib treatment, to facilitate early recognition of incipient adverse effects and initiate optimal strategies for prevention and management (with appropriate regorafenib dose holding or dose reduction, if needed).

It may be that, in patients who are frailer than those included in the clinical trials, a starting dose lower than 160 mg (e.g., 120 or 80 mg per day) might be appropriate. The dose can then be escalated within the first one or two cycles to reach the target dose of 160 mg; however, there are no data yet available to support this approach. Therefore, we currently recommend starting at the approved dose and stress the importance of assessment after 3–7 days to allow the dosing to be modified immediately as shown in Table 4 to address any evidence of toxicities. Once the patient is on a stable dose and tolerating regorafenib well, the follow-up interval can be expanded to less frequent visits (e.g., monthly or even longer after many months of benefit with good tolerance).

With the rapid growth in the number of targeted therapies being introduced into clinical practice in oncology, there is a need for high-quality evidence on the appropriate management of adverse events, supported by a greater understanding of the mechanism of action of these events. Side effects associated with targeted therapies that include VEGF inhibition appear to be relatively similar between therapeutic drugs, indicating that these adverse effects may represent a class effect resulting from inhibition of shared molecular targets. Further linking the mechanistic etiologies of these adverse events to the pathways inhibited by biologic agents represents an area of active research [15, 16].

Side effects associated with targeted therapies that include VEGF inhibition appear to be relatively similar between therapeutic drugs, indicating that these adverse effects may represent a class effect resulting from inhibition of shared molecular targets. Further linking the mechanistic etiologies of these adverse events to the pathways inhibited by biologic agents represents an area of active research.

For regorafenib, data continue to be collected for long-term follow-up analyses to assess whether delivered dose intensity correlates with therapeutic outcomes, as well as to assess interindividual differences in pharmacologic levels of regorafenib and its metabolites to guide optimal dose adjustment. Further research is also needed into the profiles of regorafenib-associated adverse effects over time; the potential impact of patients' age, ethnicity, or pharmacologic

Table 5. Grading of hand-foot skin reaction symptoms, based on National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 for palmar-plantar erythrodysesthesia syndrome [11]

Grade	Symptoms	Impact on daily activities
1	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	None
2	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain	Limiting instrumental activities of daily living
3	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain	Limiting self-care and activities of daily living
4	Not applicable	
5	Not applicable	

Table 6. Grading of liver toxicities, based on National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 for alanine aminotransferase, aspartate aminotransferase, and bilirubin [11]

Grade	ALT	AST	Bilirubin
1	>1–3 × ULN	>1–3 × ULN	>1–1.5 × ULN
2	>3–5 × ULN	>3–5 × ULN	>1.5–3 × ULN
3	>5–20 × ULN	>5–20 × ULN	>3–10 × ULN
4	>20 × ULN	>20 × ULN	>10 × ULN

Abbreviations: ALT, alanine aminotransferase, AST, aspartate aminotransferase; ULN, upper limit of normal.

biomarkers; and the effect of sequential or combination therapy with other targeted therapies (evidence from the phase III trials indicates that previous treatment with bevacizumab, imatinib, or sunitinib does not appear to lead to any "holdover" impact or worsening of adverse events on regorafenib).

Conclusion

While acknowledging that management of adverse events associated with targeted therapies is currently largely based on clinical experience rather than prospectively tested, randomized strategies, we believe that our experience has generated clinical guidance that will be helpful to clinicians treating patients with regorafenib. The adverse event profile associated with regorafenib appears to be quite predictable across tumor types and patient populations, and symptoms can be effectively managed as long as health care professionals know what to expect, assess patients early and regularly (starting within 3–4 days of treatment initiation), take prompt action, and educate, advise, and manage patients appropriately.

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Disclosures

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References

1. Wilhelm SM, Dumas J, Adnane L et al. Regorafenib (BAY 73-4506): A new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer 2011;129:245–255.

2. Bolondi L, Tak WY, Gasbarrini A et al. 6576 POSTER phase II safety study of the oral multikinase inhibitor regorafenib (BAY 73-4506) as second-line therapy in patients with hepatocellular carcinoma. Eur J Cancer 2011;47(suppl 1):S464.

3. Demetri GD, Reichardt P, Kang YK et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): An international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:295–302.

4. Eisen T, Joensuu H, Nathan PD et al. Regorafenib for patients with previously untreated metastatic or unresectable renal-cell carcinoma: A single-group phase 2 trial. Lancet Oncol 2012;13:1055–1062.

5. Furuse J, Sasaki Y, Okusaka T et al. 1236 POSTER phase I study to assess the safety, tolerability and pharmacokinetics of the multikinase inhibitor regorafenib (BAY 73-4506) in Japanese patients with advanced solid tumours. Eur J Cancer 2011;47(suppl 1):S155.

6. George S, Wang Q, Heinrich MC et al. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: A multicenter phase II trial. J Clin Oncol 2012;30:2401–2407.

7. Grothey A, van Cutsem E, Sobrero A et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303–312.

8. Mross K, Frost A, Steinbild S et al. A phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. Clin Cancer Res 2012;18:2658–2667.

9. Strumberg D, Scheulen ME, Schultheis B et al. Regorafenib (BAY 73-4506) in advanced colorectal cancer: A phase I study. Br J Cancer 2012;106:1722–1727.

10. Belum VR, Wu S, Lacouture ME. Risk of hand-foot skin reaction with the novel multikinase inhibitor regorafenib: A meta-analysis. Invest New Drugs 2013;31:1078–1086.

11. Gomez P, Lacouture ME. Clinical presentation and management of hand-foot skin reaction associated with sorafenib in combination with cytotoxic chemotherapy: Experience in breast cancer. ***The Oncologist*** 2011;16:1508–1519.

12. Grothey A, Sobrero AF, Siena S et al. Time profile of adverse events (AEs) from regorafenib (REG) treatment for metastatic colorectal cancer (mCRC) in the phase III CORRECT study. J Clin Oncol 2013;31:3637a.

13. Chu D, Lacouture ME, Fillos T et al. Risk of hand-foot skin reaction with sorafenib: A systematic review and meta-analysis. Acta Oncol 2008;47:176–186.

14. Chu D, Lacouture ME, Weiner E et al. Risk of hand-foot skin reaction with the multitargeted kinase inhibitor sunitinib in patients with renal cell and non-renal cell carcinoma: A meta-analysis. Clin Genitourin Cancer 2009;7:11–19.

15. Lacouture ME, Reilly LM, Gerami P et al. Hand foot skin reaction in cancer patients treated with the multikinase inhibitors sorafenib and sunitinib. Ann Oncol 2008;19:1955–1961.

16. Lacouture ME, Wu S, Robert C et al. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. ***The Oncologist*** 2008;13:1001–1011.

17. Bracarda S, Ruggeri EM, Monti M et al. Early detection, prevention and management of cutaneous adverse events due to sorafenib: Recommendations from the Sorafenib Working Group. Crit Rev Oncol Hematol 2012;82:378–386.

18. Manchen E, Robert C, Porta C. Management of tyrosine kinase inhibitor-induced hand-foot skin reaction: Viewpoints from the medical oncologist, dermatologist, and oncology nurse. J Support Oncol 2011;9:13–23.

19. Iijima M, Fukino K, Adachi M et al. Sorafenib-associated hand-foot syndrome in Japanese patients. J Dermatol 2011;38:261–266.

20. La Vine DB, Coleman TA, Davis CH et al. Frequent dose interruptions are required for patients receiving oral kinase inhibitor therapy for advanced renal cell carcinoma. Am J Clin Oncol 2010;33:217–220.

21. Poprach A, Pavlik T, Melichar B et al. Skin toxicity and efficacy of sunitinib and sorafenib in metastatic renal cell carcinoma: A national registry-based study. Ann Oncol 2012;23:3137–3143.

22. O'Dwyer M, Atallah E. Practical considerations for the management of patients in the tyrosine kinase inhibitor era. Semin Hematol 2009;46(suppl 3):S16–S21.

23. Shah NP, Kantarjian HM, Kim DW et al. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. J Clin Oncol 2008; 26:3204–3212.

24. Nardone B, Hensley JR, Kulik L et al. The effect of hand-foot skin reaction associated with the multikinase inhibitors sorafenib and sunitinib on health-related quality of life. J Drugs Dermatol 2012; 11:e61–e65.

25. Anderson R, Jatoi A, Robert C et al. Search for evidence-based approaches for the prevention and palliation of hand-foot skin reaction (HFSR) caused by the multikinase inhibitors (MKIs). ***The Oncologist*** 2009;14:291–302.

26. Lacouture ME, Maitland ML, Segaert S et al. A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. Support Care Cancer 2010;18: 509–522.

27. Ren Z, Zhu K, Kang H et al. A randomized controlled phase II study of the prophylactic effect of urea-based cream on the hand-foot skin reaction associated with sorafenib in advanced hepatocellular carcinoma. J Clin Oncol 2012;30:4008a.

28. Choueiri TK, Mayer EL, Je Y et al. Congestive heart failure risk in patients with breast cancer treated with bevacizumab. J Clin Oncol 2011;29:632–638.

29. Schutz FA, Je Y, Azzi GR et al. Bevacizumab increases the risk of arterial ischemia: A large study in cancer patients with a focus on different subgroup outcomes. Ann Oncol 2011;22:1404–1412.

30. Cheng H, Force T. Molecular mechanisms of cardiovascular toxicity of targeted cancer therapeutics. Circ Res 2010;106:21–34.

31. Desai J, Yassa L, Marqusee E et al. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. Ann Intern Med 2006;145:660–664.

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