Management of Sorafenib-Related Adverse Events: A Clinician's Perspective

Marcia S. Brose,[a] Catherine T. Frenette,[b] Stephen M. Keefe,[c] and Stacey M. Stein[d]

Sorafenib, a tyrosine kinase inhibitor, is approved for the treatment of patients with unresectable hepatocellular carcinoma (HCC) and advanced renal cell carcinoma (RCC). It is being evaluated in phase II and III clinical trials, which include treatment as a single agent (locally advanced/metastatic radioactive iodine-refractory differentiated thyroid cancer [DTC]), as part of multimodality care (HCC), and in combination with chemotherapeutic agents (metastatic breast cancer). Sorafenib-related adverse events (AEs) that commonly occur across these tumor types include hand–foot skin reaction (HSFR), rash, upper and lower gastrointestinal (GI) distress (ie, diarrhea), fatigue, and hypertension. These commonly range from grade 1 to 3, per the Common Terminology Criteria for Adverse Events (CTCAE), and often occur early in treatment. The goal for the management of these AEs is to prevent, treat, and/or minimize their effects, thereby enabling patients to remain on treatment and improve their quality of life. Proactive management, along with ongoing patient education (before and during sorafenib treatment), can help to effectively manage symptoms, often without the need for sorafenib dose modification or drug holidays. Effective management techniques for common sorafenib-related AEs, as well other important disease sequelae not directly related to treatment, are presented. Recommendations and observations are based on physician/author experience and recommendations from published literature.
Semin Oncol 41:S1-S16

[a]Assistant Professor, Director of the Thyroid Cancer Therapeutics Program, Department of Otorhinolaryngology: Head and Neck Surgery, and the Division of Hematology/Oncology, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA.
[b]Medical Director of Liver Transplantation, Center for Organ and Cell Transplantation, Scripps Clinic, San Diego, CA.
[c]Assistant Professor, Division of Hematology/Oncology, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA.
[d]Assistant Professor of Medicine, Department of Medical Oncology, Yale School of Medicine, New Haven, CT.
This supplement was funded by Onyx Pharmaceuticals Inc. and Bayer Healthcare. Medical writing services and editorial support were provided by Blue Momentum, a division of KnowledgePoint360 Group.
Conflicts of interest: Marcia S. Brose: honoraria and research funding from Onyx Pharmaceuticals Inc. and Bayer Healthcare. Catherine T. Frenette: Speaker's bureau for Onyx Pharmaceuticals Inc. Stephen M. Keefe: No potential conflict of interest relevant to this article was reported. Stacey M. Stein: Honoraria from Onyx Pharmaceuticals and Bayer Healthcare.
Address correspondence to Catherine T. Frenette, MD, Medical Director of Liver Transplantation, Center for Organ and Cell Transplantation, Scripps Clinic, 10666 N Torrey Pines Rd N200, San Diego, CA 92037. E-mail: Frenette.Catherine@scrippshealth.org
0093-7754

http://dx.doi.org/10.1053/j.seminoncol.2014.01.001

Sorafenib, an oral multikinase inhibitor, is approved by the US Food and Drug Administration for the treatment of patients with unresectable hepatocellular carcinoma (HCC) and advanced renal cell carcinoma (RCC).[1] In phase III studies, patients treated with single-agent sorafenib showed a significant advantage for progression-free survival (PFS) compared with placebo (in RCC) and an overall survival benefit (in HCC).[2–6] An overall survival benefit was also observed in patients with RCC when data were censored for placebo-assigned patients who had crossed over to sorafenib treatment.[6] Promising results from phase II studies with single-agent sorafenib in patients with iodine-refractory differentiated thyroid cancer (DTC; median PFS = 79 weeks)[7–10] prompted initiation of the randomized, placebo-controlled, phase III DECISION study, which reached completion in December 2012.[11,12]

Sorafenib is currently being evaluated in other phase II and phase III clinical trials, which include treatment as part of multimodality care (HCC) and in combination with chemotherapeutic agents (metastatic breast cancer).[13]

The recommended starting dose for sorafenib in patients with HCC and RCC is 400 mg (two tablets)

given orally twice a day, without food.[1] In the recently reported final analysis of GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of Its Treatment With Sorafenib), a non-interventional phase IV study in patients with HCC, data showed that the average daily dose of sorafenib was slightly higher in patients with Child-Pugh B (741.5 mg) than with Child-Pugh A (677 mg), but overall, dosing was generally consistent across patients regardless of Child-Pugh status.[14] In the phase II and phase III DTC studies, the starting dose is 400 mg, twice a day.[7–10] However, treatment interruptions and/or dose reductions may be warranted to manage some adverse events (AEs). The most common AEs related to sorafenib treatment that may impact quality of life (QOL) include hand–foot skin reaction (HFSR), rash (often occurring as a papular, erythematous eruption that can involve extremities, as well as the trunk), upper and lower gastrointestinal (GI) distress, and fatigue[1,15] (Tables 1 and 2).

Hypertension (HTN), another AE that is commonly observed, does not directly affect QOL, while AEs that are less common or are rare but of concern include cardiovascular events (other than HTN, and including congestive heart failure, myocardial ischemia and/or infarction, hypertensive crisis, and QT prolongation), portal HTN and variceal bleeding, wound healing, and squamous cell carcinoma of the skin.[1]

Patients with visceral-organ (RCC and HCC) and non–visceral-organ (DTC) disease may have different challenges (eg, patients with HCC often have underlying cirrhosis, and patients with RCC may have HTN and hypercalcemia, while patients with DTC may have hypocalcemia). Furthermore, with declining health, there is an increase in AEs overall,[16,17] which may or may not be directly related to treatment with sorafenib.

In contrast, patients with non–visceral-organ disease (ie, DTC) are relatively healthy and may be treated long-term with sorafenib. Therefore, the approach to management of AEs may vary by patient population and by length of treatment. Regardless of the patient population, however, the successful management of AEs may allow patients to tolerate the full dose of sorafenib, thereby enabling patients to remain on the sorafenib treatment and maintain a good QOL.

Data presented here include safety outcomes from the pivotal phase III sorafenib (single-agent) studies that supported its approval by the US Food and Drug Administration for use in patients with HCC and RCC. This article also includes outcomes from the phase II DTC (single-agent) trial, which has been completed and published, met its primary end point, and led to the phase III study. Recommendations for the management of common AEs in patients taking sorafenib are provided per the clinical experience of the authors, as well as per further guidance from the literature.

SORAFENIB-RELATED AEs

Hand–Foot Skin Reaction

HFSRs, which are usually Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2 (see Table 3), can have a significant effect on patient QOL. HFSRs generally appear within the first 6 weeks of sorafenib treatment[1] but may occur as early as 1–2 weeks following treatment initiation.[1,18]

Management Approach

The main goal for the management of HFSR is to allow patients to maintain their sorafenib dose for as long as is indicated. This may be accomplished through patient education and proactive management, which often include keeping hands and feet moisturized with a thick urea-based cream,[19] removing thick calluses (hyperkeratosis), wearing comfortable shoes with minimal pressure points, and avoiding hot water[18,20–24] (see Table 3). The cornerstone of management is to keep skin well hydrated, remove calluses regularly, and use pain medication as needed.

Based on the clinical experience of the authors, it is highly recommended that clinicians see patients in 2-week intervals for the first 2 months following sorafenib initiation to proactively manage HFSR. With grade 1 or 2 HFSR, patients generally can continue sorafenib treatment without any changes to dose or administration.[1] Intolerable grade 2 HFSR that does not improve following one or two dose holidays or a grade 3 episode (eg, patient unable to walk) may require dose reduction.[25] HFSR does not tend to worsen after 3 months of sorafenib treatment. In a subgroup analysis of the phase III TARGET (Treatment Approaches in Renal Cancer Global Evaluation Trial) trial in patients with RCC, the overall incidence of HFSR tended to peak after the first cycle (29%), with fewer cases reported subsequently (16%, 3%, and 1%, during cycles 2, 3, and 4, respectively). Grade 3/4 HFSR, when it did occur, also developed most frequently in early cycles (cycles 1–5 and 7).[26] In a phase II trial of patients with DTC who were treated with sorafenib (N = 55), HFSR severity peaked at treatment cycle 2 and declined by cycle 6 (39% and 10% of patients had grade 2–3 HFSR in cycles 2 and 6, respectively); 17 patients (31%) required dose reduction due to HSFR.[27] With proper management, beginning at the earliest signs of HFSR, patients may be guided over the toughest period and continue therapy, without sorafenib dose reductions or interruptions in therapy.[28]

Table 1. Incidence of Adverse Events and Laboratory Abnormalities in Patients With Visceral-Organ Disease, by CTCAE Grade 3 in the Pivotal Phase III Studies*

	HCC†,1,2				RCC‡,1,6					
	Sorafenib (n = 297)		Placebo (n = 302)		Sorafenib (n = 452)		Placebo (n = 451)		Crossover From Placebo to Sorafenib (n = 216)	
Parameter, %	**Any Grade**	**Grades 3/4**	**Any Grade**	**Grades 3/4**	**Any Grade**	**Grades 3/4**	**Any Grade**	**Grades 3/4**	**Any Grade**	**Grades 3/4**
Adverse events										
Dermatologic										
HFSR	21	8	3	<1	33	6	8	<1	37	7
Rash/desquamation	19	1	14	0	31	0	4	0	34	0
Alopecia	14	0	2	0	31	0	4	0	34	0
Gastrointestinal										
Diarrhea	55	10	25	2	48	3	11	1	48	5
Nausea	24	1	20	3	19	<1	12	<1	14	1
Vomiting	15	2	11	2	12	1	6	<1	9	1
Anorexia	229	3	18	3	14	<1	7	1	16	1
Constipation	14	0	10	0	7	0	4	0	7	0
Constitutional										
Fatigue	46	10	45	14	29	3	16	1	25	5
Weight loss	30	2	10	11	8	1	1	0	11	1
Cardiovascular										
Hypertension	9	4	4	1	17	4	1	0	13	4
Laboratory abnormalities										
Hypophosphatemia	35	11	11	3	NR	NR	NR	NR	NR	NR
Hypocalcemia	27	2	15	1	NR	NR	NR	NR	NR	NR

* The pivotal phase III studies that led to approval of sorafenib by the US Food and Drug Administrator are included in this table;
† Includes patients in both the SHARP (N = 599) and the Asia-Pacific (N = 224) clinical trials. The dosing and administration in both trials was oral sorafenib 400 mg or placebo, twice a day, in 6-week cycles.
‡ In the TARGET trial, patients with RCC received continuous, twice-a-day treatment with either sorafenib 400 mg or placebo. After a planned analysis, 48% of patients from the placebo group crossed over to sorafenib, after a progression-free survival advantage was demonstrated in the sorafenib group.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; HCC, hepatocellular carcinoma; HFSR, hand–foot skin reaction; NR, data not reported; SHARP, Sorafenib HCC Assessment Randomized Protocol; TARGET, Treatment Approaches in Renal Cancer Global Evaluation Trial.

Table 2. Incidence of Adverse Effects and Laboratory Abnormalities in Patients With Non–Visceral-Organ Disease, by CTCAE Grade 3, in the Phase II DTC Study*

	DTC[†,10] Sorafenib (N = 33)	
Adverse Events, %	Grades 1/2	Grades 3/4
Dermatologic		
HFSR	83[‡]	10[‡]
Rash/ desquamation	70	10
Alopecia	43	0
Gastrointestinal		
Diarrhea	73	7
Nausea/vomiting	30	0
Anorexia	17	3
Constipation	7	0
Constitutional		
Fatigue	60	3
Weight loss	50	10
Cardiovascular/ pulmonary		
Hypertension	30	13

* Only the phase II single-agent sorafenib study, which was completed, met its primary end point, was published, and led to a phase III study, is included in this table.
† Patients in the DTC phase II study received sorafenib 400 mg orally twice a day;
‡ Palmar–plantar erythema.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; DTC, radioactive iodine-refractory differentiated thyroid cancer; HFSR, hand–foot skin reaction.

Rash

Rash is common in patients treated with sorafenib[2,6,10] (see Tables 1 and 2) and presents as a macular or papular rash over the extremities and sometimes over the trunk, often occurring in the first month of treatment.[26] In the phase II sorafenib DTC study, rash severity peaked at cycle 1 and declined by cycle 3 (19% and 5% of patients had grade 2–3 rash in cycles 1 and 3, respectively).[27] Overall, the severity and prevalence of skin AEs (including rash and HFSR) reached a steady state following cycle 12. Of the 30 (55%) patients who required dose reductions because of skin AEs, 31% were able to resume their full dose of sorafenib by the end of the study.

Management Approach

Most rashes are not painful and resolve on their own, and patient education is all that is required. Rashes that cause discomfort may respond to a change to mild, perfume-free soaps; increased emollient applications; avoidance of hot water; and/or wearing loose, natural fabric clothing.[29] Published data suggest that topical corticosteroids may have some efficacy early in therapy when the rash is mild. In addition, although antihistamines (eg, Benadryl [McNeil-PPC, Inc., Fort Washington, PA]) may be considered, they have shown minimal efficacy.[30] Severe rash in four patients treated by the authors was resolved by a short course of oral corticosteroids (unpublished data); however, no clinical trial data exist at this time to support the use of this approach.

Upper and Lower GI Distress

Epigastric Pain: Dyspepsia

Upper GI effects are often caused by reflux or dyspepsia, and grade 1 or grade 2 dyspepsia symptoms commonly occur in patients treated with sorafenib[1,2,6,10] (see Tables 1 and 2). Epigastric pain, which may affect patients over the long term, can cause appetite loss and anorexia, which may lead to (sometimes severe) weight loss.

Management Approach. Management of dyspepsia (Table 4) is generally similar between tumor types and may be controlled via a low-fiber diet, changes in the timing of sorafenib dosing to always occur before a meal, and the use of supplements, such as probiotics and digestive enzymes. If these approaches are ineffective, the addition of a proton pump inhibitor[22] and sucralfate (Carafate; Aptalis Pharma US, Bridgewater, NJ) suspension, which is indicated for the treatment of peptic ulcers[37] and also has been shown to be effective in patients with gastroesophageal reflux disease (GERD),[38] may be helpful. However, recent recommendations based on strength of evidence for the superiority of proton pump inhibitors over sucralfate for GERD management indicates that there may be little role for sucralfate in the nonpregnant patient with GERD.[39]

Diarrhea

Diarrhea is often associated with sorafenib therapy and is most commonly CTCAE grade 1/2[1,2,6,10] (see Tables 1 and 2). Diarrhea may begin early in treatment (immediately or up to 8 weeks) in patients with visceral-organ disease. In the TARGET trial in patients with RCC, diarrhea tended to develop early (within 1 month), and the overall incidence of diarrhea rose during early cycles of sorafenib treatment (23%, 23%, 29%, and 39% in cycles 1, 2, 3, and 4, respectively).[26] However, in patients with DTC, diarrhea often occurs much later; approximately 3–4 months after the initiation of sorafenib treatment. In DTC, onset of diarrhea may be slow and then remain constant, aggravated primarily by poor dietary choices. The authors have observed that, regardless of tumor type (RCC, HCC, DTC), episodes of diarrhea occur intermittently (eg, 2–3 days per week) in the majority (80%) of patients; however, in HCC,

Table 3. Recommendations for the Prophylaxis and Management of HFSR

Timing	Management Recommendations for HFSR Toxicity[18–24]
Prior to sorafenib treatment	1. Baseline physical for preexisting hyperkeratosis 2. Patient education (prevention and management) 3. Frequent (bid) emollients used on hands and feet to maintain skin hydration 4. Manicure/pedicure to control calluses 5. Use a keratolytic agent on calluses bid to aid exfoliation (20%–40% urea-based creams (eg, Carmol 40 [Doak Dermatologics, Fairfield, NJ] with Keralac [Doak Dermatologics, Fairfield, NJ])* 6. Protect pressure points and tender areas of feet with insole cushions, shock-absorbing soles, soft/comfortable shoes (eg, Crocs [Crocs Retail, Inc., Niwot, CO]), and so forth
Throughout sorafenib treatment, regardless of HFSR toxicity grade (0–4)	Continue with #2–#6 above, plus… 7. Monitor patient weekly during the first 6 weeks following sorafenib treatment initiation 8. Avoid hot water 9. Wear thick cotton gloves and/or socks 10. Wear cotton gloves/socks at night after applying emollients to prevent further injury and retain moisture 11. Foot soaks in cool water with magnesium sulfate to reduce pain and soften calluses

During sorafenib treatment, by CTCAE (v3) toxicity grade	Recommendations, Regardless of Tumor Type	
	First Approach	**Second Approach**
HFSR grade 1 Mild: minimal skin changes or dermatitis (eg, erythema) without pain	Follow recommendations 2–11 above, plus… • Two-week follow-up	• Possible topical therapy for symptomatic relief • Dose modification *not* recommended
HFSR grade 2 Moderate: skin changes (eg, peeling, blisters, bleeding, edema) or pain, not interfering with function	• Follow "*throughout treatment*" recommendations above, plus… • One-week follow-up • Clobetasol 0.05% ointment, bid, applied to erythematous areas • Topical analgesic (eg, lidocaine 2%) for pain	• *Dose modification usually not needed* • If dose modification is warranted, consider 50% dose reduction (from 800 to 400 mg qd) 7–28 days until the HFSR reaches grade 1 or 0, and then resume full dosing • If not resolved, interrupt treatment until HFSR resolved, and then resume at a reduced dose (400 mg qd)† • Repeat steps 2 or 3 for second or third occurrence • Upon fourth occurrence, discontinue sorafenib based on clinical judgment and patient preference

Table 3 (continued)

During sorafenib treatment, by CTCAE (v3) toxicity grade	Recommendations, Regardless of Tumor Type	
	First Approach	Second Approach
HFSR grade 3 Severe: ulcerative dermatitis or skin changes with pain that interferes with function	Follow recommendations 2–11 above, plus… • One-week follow-up • Topical therapy for symptomatic relief (cortisone cream) • Systemic strategies to reduce symptoms, eg, pyridoxine (50–150 mg/day), may be of benefit	• *Dose modification MAY be warranted* • Interrupt treatment for ≥7 days until HFSR reaches grade 1 or 0 • Resume treatment at 50% of full dose (400 mg qd) • Monitor patient for toxicity; if none, escalate to full dose • For second occurrence, reduce dosage to 400 mg qd or once every other day • For third or fourth occurrence, treatment may be resumed based on clinical judgment or patient preference

* With frequent cream usage, there is an increased risk of tinea pedis ("athlete's foot"), which should be distinguished from HFSR.
† To date, there is no evidence to support the relation of sorafenib drug interruptions with HFSR toxicity and clinical outcomes.
Abbreviations: bid, 2 times per day; CTCAE, Common Terminology Criteria for Adverse Events; DTC, radioactive iodine-refractory differentiated thyroid cancer; HCC, hepatocellular carcinoma; HFSR, hand-foot skin reaction; NSAID, nonsteroidal anti-inflammatory drug; qd, once per day; RCC, renal cell carcinoma.

diarrhea may also occur more frequently (up to 10–20 times per day in approximately 5% of patients) (unpublished author data). Concurrent use of the disaccharide lactose for treatment of hepatic encephalopathy in patients with HCC may provide another level of GI distress, as it is commonly a source of diarrhea.[40] Uncontrolled diarrhea has important implications for dehydration and electrolyte imbalance,[31,34] as well as having an obvious impact on patients' QOL[31,35] and their ability to tolerate their cancer treatment.

Management Approach. The treatment approach for diarrhea (see Table 4) is similar across tumor types and generally includes dietary adjustments, symptomatic control of diarrhea, and monitoring/managing electrolytes. In the experience of the authors, the need to reduce or interrupt the sorafenib dose for grade 1 or 2 events is rare. When symptomatic treatment for diarrhea is needed, most patients are able to obtain good control on a single drug, such as loperamide, which can be increased until control is achieved. However, for patients with HCC who are taking lactulose, their dose may be decreased.

Fatigue

Fatigue was frequently reported in patients in the sorafenib phase III (HCC and RCC) and phase II (DTC) clinical studies[2,6,10] (see Tables 1 and 2). Fatigue is generally self-limited, commonly occurring in the first 4–6 months of sorafenib treatment and often resolving after approximately 5–6 months on treatment (author experience). In patients with HCC, however, it is often unclear whether the fatigue is drug-related or due to the underlying liver disease or other cancer treatment, such as recent or ongoing transcatheter arterial chemoembolization procedures.[41]

Management Approach. Because fatigue may be symptomatic of other underlying issues, patients should be evaluated for other treatable contributing factors, including emotional distress (ie, depression, anxiety), adverse events of other medications, pain, anemia, sleep disturbances, nutritional issues (ie, weight or food intake changes, imbalances in fluids/electrolytes), decreased physical activity, and comorbid conditions (ie, alcohol/substance abuse; infection; cardiac, endocrine, gastrointestinal, hepatic, neurologic, pulmonary, or renal dysfunction).[42] Medication is generally not needed for patients with fatigue.[42] Unlike HFSR and diarrhea, fatigue associated with sorafenib is likely to resolve around month 6 without treatment or dose adjustment. Educating patients regarding what to expect and how to adjust their schedules accordingly is usually the key to managing symptoms of fatigue (Table 5).

Hypertension and Other Cardiovascular Issues

Hypertension

HTN has been reported to occur at a higher incidence in patients with DTC[10] than in patients

Table 4. Recommendations for the Management of Lower and Upper GI Distress

	Management Recommendations for Diarrhea and Dyspepsia			
	Diarrhea[1,31–36]		Dyspepsia[22,38]	
	General	Tumor-Specific	General	Tumor-Specific
General	• Treatment is often symptomatic • Patient education and proactive management is key • Sorafenib dose reduction is rarely needed for grade 1 or grade 2 diarrhea • Note that drugs may change taste, which can affect eating habits • Chronic diarrhea can lead to dehydration and electrolyte imbalances	• HCC: remind patients to adjust their lactulose as needed	• Dyspepsia can usually be managed, and sorafenib dose reduction is rarely required • Epigastric pain, which may affect patients over the long term, affects appetite, which can lead to (sometimes severe) weight loss	
Patient education	• Prior to and throughout sorafenib treatment, educate patients regarding diarrhea onset and management, as well as dietary restrictions		• Prior to and throughout sorafenib treatment, educate patients as to dietary restrictions	
Patient monitoring	• Monitor/manage electrolytes in patients who may be dehydrated • Patients should alert their healthcare team regarding changes in bowel habits • Sharp pains in lower gut (ie, cramping, abdominal pain) or an inability to pass stool should be evaluated for risk of GI perforation (very rare), particularly in patients with a history of diverticulitis or diverticulosis		• Patients should alert their healthcare team regarding onset of GI distress	

Table 4 (continued)

	Management Recommendations for Diarrhea and Dyspepsia			
	Diarrhea[1,31–36]		Dyspepsia[22,38]	
	General	Tumor-Specific	General	Tumor-Specific
	• Assess for *Clostridium difficile* infection or spontaneous peritonitis (not related to sorafenib treatment)			
Sorafenib dose timing with food/water			• Timing of sorafenib dosing with food differs by tumor type	• **RCC and HCC:** Take sorafenib dose with bread or crackers • **DTC**: Take sorafenib 30 minutes (instead of 1 hour) following a meal
Diet	• Avoid caffeine, dairy, and greasy foods (worsens GI distress) • Adding or avoiding fiber is dependent on tumor type • Adverse foods can be patient-specific: it is recommended that patients keep food diaries	• HCC: adding fiber to the diet (eg, Benefiber supplement [Novartis Consumer Health, Parsippay, NJ]) may be helpful • **DTC**: a diet low in fiber is recommended	• Follow recommendations for diarrhea • Minimize intake of gas-producing foods • Avoid carbonated drinks	
Supplementation	• Replace lost calcium with supplementation		• Supplement with lactinex granules or alternate with a probiotic for 2–4 weeks to control the increasing gas and discomfort, as well as from possible pancreatic insufficiency (in HCC) and change in gut flora	

Table 4 (continued)

	Management Recommendations for Diarrhea and Dyspepsia			
	Diarrhea[1,31–36]		Dyspepsia[22,38]	
	General	Tumor-Specific	General	Tumor-Specific
			• Probiotics will help to aid digestion and restore normal GI flora	
Treatment	• Antimotility agents (eg, loperamide [Imodium A-D; McNeil-PPC, Inc., Fort Washington, PA]) are an effective way to treat diarrhea, rather than waiting to see if dietary changes are effective • Prior to treatment, patients should have loperamide on hand • Intermittent loperamide treatment (as needed, followed by two tablets every 4 hours) can normalize motility and control diarrhea • Take loperamide at a dose of 4 mg, followed by 2 mg every 4 hours or after each loose stool • Loperamide should be taken at the *onset* of diarrhea, with or without food • With worsening diarrhea, a standing dose of loperamide, titrated to 12 pills/day is reasonable • Loperamide (2 mg) may be taken prophylactically 30 minutes before the scheduled sorafenib dose in patients who		• If dietary changes and supplementation are ineffective, follow with a proton pump inhibitor (bid: 2 hours before or after sorafenib dosing), on which the patient can remain for the duration of their sorafenib therapy • Sucralfate (Carafate; Aptalis Pharma US, Bridgewater, NJ) suspension, an antiulcer medication, taken qd, may also be helpful	

Table 4 (continued)

	Management Recommendations for Diarrhea and Dyspepsia			
	Diarrhea[1,31–36]		Dyspepsia[22,38]	
	General	Tumor-Specific	General	Tumor-Specific
	experienced diarrhea with previous sorafenib doses • If loperamide is ineffective, diphenoxylate/atropine is recommended in a similar dose-escalation fashion as loperamide			
Other medications	• For refractory diarrhea, opiates (eg, codeine) may be used for their antimotility effect on the GI tract • Cholestyramine (Questran; PAR Pharmaceutical, Spring Valley, NY), 4 g/tid, which binds bile acids, may be helpful in treating diarrhea in some patients; however, it should be taken separately from other medications to avoid interaction	*Cholestyramine* • **DTC**: cholestyramine is contraindicated as it negatively impacts synthroid/ levothyroxine replacement. If used, take at night to minimize drug interactions • Cholestyramine is also contraindicated in patients with complete biliary obstruction	• **HCC and RCC:** Avoid NSAIDS and aspirin	
Sorafenib dose reductions	• Sorafenib dose reduction (to 400 mg qd or every other day) or interruption may be necessary for unmanageable or grade 3 or 4 diarrhea until diarrhea returns to baseline or grade 1			

Abbreviations: bid, twice a day; DTC, radioactive iodine-refractory differentiated thyroid cancer; GI, gastrointestinal; HCC, hepatocellular carcinoma; NSAID, nonsteroidal anti-inflammatory; qd, once per day; RCC, renal cell carcinoma; tid, three times a day.

with HCC[2] and RCC[6] (see Tables 1 and 2); however, this may be the product of longer treatment duration in patients with DTC. Also, it should be noted that data for DTC are phase II, while data from the HCC and RCC trials are phase III and thus more mature. Recent data from a retrospective cohort study of 101 patients with advanced solid tumors who were treated with sorafenib (400 mg twice daily for ≥12 weeks) in a randomized discontinuation trial showed that an increase in systolic blood pressure (SBP) as well as the mean amplitude of change were significantly greater in RCC patients than in non-RCC patients.[43] In this study, 72% and 32% of RCC and non-RCC patients, respectively, developed an

Table 5. Recommendations for the Management of Fatigue

	Fatigue[42] (author experience)	
Parameter	**General**	**Tumor-Specific**
Dose reductions	• Dose reductions not needed	
Adjust daily schedules and sorafenib dose timing	• Adjust daily schedules accordingly, until the fatigue passes • Taking sorafenib in the evening (rather than during the day) may minimize daytime fatigue	
Stimulants	• Stimulants are not recommended; however, patients can incorporate caffeine into their diet	
Screen for depression	• Patients with long-term fatigue should also be screened for depression	
Exercise may be helpful	• For patients that are well enough, exercise (eg, walking) may help with fatigue • Weight-bearing exercise may also help replace lost skeletal muscle mass, which may be lost following prolonged GI distress. This tends to concomitantly lift fatigue, depression and, often, diarrhea	• **HCC:** patients are often not well enough to exercise strenuously but should be encouraged to do some mild exercise daily
Monitor electrolytes and hemoglobin	• Ensure electrolytes and hemoglobin are at normal levels, monitor at every visit; electrolyte imbalance from diarrhea/nonhydration may cause depression • Monitor for hypophosphatemia, which worsens fatigue • Monitor hemoglobin levels • Monitor TSH levels every quarter: sorafenib has resulted in hypothyroidism and subclinical hypothyroidism. For clinical hypothyroidism, treat with thyroid replacement medication	
Control encephalopathy		• **HCC:** control encephalopathy, which may also impact fatigue

Abbreviations: GI, gastrointestinal; HCC, hepatocellular carcinoma; TSH, thyroid-stimulating hormone.

increase in SBP of at least 20 mm Hg (mean increase: 30 mm Hg [RCC] *v* 19 mmHg [non-RCC]); $P < .003$.

HTN usually occurs in the first 6 weeks of treatment with sorafenib[1]; therefore, blood pressure (BP) should be monitored regularly (at least once a week) at the start of sorafenib therapy. Although some patients are hypertensive before treatment with sorafenib and may already be taking antihypertensive medications, patients with advanced cirrhosis (eg, in HCC) are characteristically hypotensive as a result of peripheral vasodilation, which occurs in approximately half of hospitalized patients with cirrhosis and ascites.[44,45] Therefore, it is possible that sorafenib may actually help to normalize BP in some of these patients. Diarrhea, which may lead to dehydration and hypotension, can mask HTN, which may reappear when diarrhea is corrected. Once HTN is well controlled, it often does not need to be readdressed, and the dose of sorafenib does not generally have to be adjusted.[46]

Other Cardiovascular Risks

There are additional cardiovascular risks with the long-term (>1 year) use of sorafenib; these include both thromboembolic and cardiac ischemic events. The relative risk of tyrosine kinase inhibitor–associated arterial thromboembolic events (ATEs) appears to differ by tumor type. In large clinical trials of patients with HCC (N = 297) and RCC (N = 451), the relative risk (95% confidence interval) of acquiring an ATE compared with placebo was 2.03 (0.62–6.68) and 6.00 (1.35–26.66), respectively. The difference compared with control groups was significant in patients with RCC ($P = .019$) but not with HCC ($P = .242$).[47] In a study of cardiac safety in patients with RCC, a 2% incidence in left ventricular ejection fraction decline was observed in patients with RCC.[48]

Management Approach. For HTN and all cardiovascular AEs, patient education is extremely important. Patients should be continually reminded of cardiac adverse events and to report symptoms to their healthcare team immediately. Treatment recommendations may vary by tumor type (Table 6); however, HTN should generally be managed according to standard medical practice,[1] following guidelines by the Joint National Committee for the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).[49]

Portal HTN and Variceal Bleeding

Variceal bleeding, which is associated with portal HTN, is HCC-specific and is not sorafenib-related. Although uncommon, variceal bleeds can be significant in patients with HCC and may be caused by

Table 6. Recommendations for the Management of HTN and Other Cardiovascular Adverse Events

Parameter	Management recommendations[1,22] (author experience)	
	General	Tumor-specific
Hypertension	• Monitor blood pressure weekly during the first 6 weeks of sorafenib treatment • Education: all patients should check their blood pressure a few times a week and report changes to their healthcare team. *"Healthy remembrance": a headache of 3 days' duration can signal HTN* • If patients have HTN before starting sorafenib, bring under control with antihypertensive medication • Patients are generally not refractory to antihypertensive treatment; therefore, there is usually no cause to discontinue sorafenib treatment	*Antihypertensive medication* • **HCC**: use nonselective beta-blockers (ie, carvedilol, nadolol, or propranolol), followed by calcium channel blockers if noneffective. There is an added benefit of decreased portal pressure in patients with liver disease with use of nonselective beta-blockers • **RCC**: dihydropyridine calcium channel blockers (eg, amlodipine) are commonly used in the setting of RCC • **DTC**: begin with a beta-blocker
Other cardiovascular risks	• May perform a stress test for some patients with a cardiac history (before, at 6 months, and 1 year after starting sorafenib therapy)	

Abbreviations: DTC, radioactive iodine-refractory differentiated thyroid cancer; HCC, hepatocellular carcinoma; HTN, hypertension; RCC, renal cell carcinoma.

cirrhosis or hepatitis C infection in the presence of cirrhosis. In patients with HCC enrolled in the phase III SHARP (Sorafenib HCC Assessment Randomized Protocol) trial, the risk of variceal bleeds was no different between the sorafenib (2%) and placebo (4%) groups.[2] Overall, the risk for bleeding events in all tumor types (including HCC, RCC, and DTC) has been rare; therefore, it should not be a reason for withholding sorafenib treatment or surgery (Table 7). Routine variceal screening and prophylaxis as standard of care in patients with cirrhosis should be employed.

Wound Healing

Although the risk of poor wound healing is low with sorafenib therapy, it still elicits concern among clinicians. Fistula formation, which occurs in <1% of patients with HCC and RCC[1] can often appear at the site of prior surgery and radiation. Primarily out of concern for decreased perfusion leading to poorer wound healing, recommendations are to stop sorafenib treatment 24 hours before surgery[1] and restart once wound healing is well established. The authors note that, contrary to recommendations in the US prescribing information,[1] they have not stopped sorafenib therapy before surgery (eg, emergency surgery) and have not observed any issues with wound healing.

Other AEs

Mucositis complications and oropharyngeal toxicities (usually grade 1 or grade 2) have been observed in 30% to 40% of patients with RCC,[6] as well as in 47% of patients with DTC,[10] and may manifest as mouth ulcers, mouth sensitivities, and lesions in the mouth. "Magic" mouthwash (lidocaine, Maalox [Novartis Consumer Health, Parsippany, NJ] plus sucralfate to reduce the sensitivity of the mucosa) or salt water rinses may provide symptomatic relief. Data from a randomized, double-blind clinical trial showed that 142 of 200 (71%) patients with chemotherapy-induced mucositis obtained relief (disappearance of signs and symptoms of mucositis) within 12 days of treatment with the

Table 7. Recommendations for the Management of Portal HTN and Variceal Bleeds in Patients With HCC

Parameter	Management recommendations	
	General	Tumor-specific
General	• The risk for bleeding events is low; therefore, it should never be a reason for withholding therapy	• In cirrhosis, variceal bleeds do not seem to correlate with platelet count[50]; therefore, it is safe to continue with sorafenib treatment • **HCC:** sorafenib decreases portal pressure[51]
Sorafenib treatment	• Depending on the tumor type, treatment should not be withheld pending assessment for varices • Complete variceal eradication prior to sorafenib treatment is not required	• In end-stage disease, the benefits of treatment may outweigh the risk of withholding treatment • For non–end-stage disease, a drug holiday may be recommended
Portal hypertension management	• All patients with cirrhosis should be screened for esophageal varices as standard of care • Nonselective beta-blockers (eg, carvedilol, propranolol and nadolol) are commonly used for primary prophylaxis of variceal bleeding[52]	
Education	• Patients should be reminded to remain vigilant and immediately report symptoms to their healthcare team after 1 year of treatment	

Abbreviations: HCC, hepatocellular carcinoma; HTN, hypertension.

use of either magic mouthwash; salt and sodium bicarbonate; or chlorhexidine. However, differences in efficacy between types of mouthwash were not statistically significant.[53] There also may be a concern that the numbing effect from the lidocaine in magic mouthwash may make swallowing difficult for some patients.[54]

CONCLUSIONS

Proactive and effective management of AEs that may occur during treatment with sorafenib will allow patients to remain on their prescribed dose, thereby maximizing its therapeutic benefit. For patients with RCC and HCC, in the absence of cirrhosis or with Child-Pugh A cirrhosis and good performance status, starting on a full sorafenib dose is recommended.[1] The starting dose under review in patients with DTC is also 400 mg twice per day.

Physicians can help patients by reviewing potential AEs with them prior to beginning therapy, emphasizing effective management strategies. Patients should be encouraged to call their healthcare team between visits to quickly address issues of toxicity. Overall, patient education and empowerment, both prior to and during sorafenib therapy, is of primary importance in helping to prevent and manage AEs, such as HFSR and diarrhea. Patients also should be reminded to proactively monitor their BP and, with long-term sorafenib use, remain aware of and report cardiac symptoms without delay.

Through effective management of AEs that commonly occur during treatment with sorafenib, patients may enjoy a better QOL and receive full benefit of their sorafenib treatment.

REFERENCES

1. Nexavar (sorafenib) tablets prescribing information. Wayne, NJ; Bayer HealthCare Pharmaceuticals, Inc; 2012.
2. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378–90.
3. Cheng Al, Kang Yk, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10:25–34.
4. Cheng AL, Guan Z, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: subset analyses of the phase III Sorafenib Asia-Pacific trial. Eur J Cancer. 2012;48:1452–65.
5. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356:125–34.
6. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol. 2009;27:3312–8.
7. Ahmed M, Barbachano Y, Riddell AM, Whittaker S, Newbold K, Harrington K, et al. An open-labeled phase 2 study evaluating the safety and efficacy of sorafenib in metastatic advanced thyroid cancer [abstract]. Ann Oncol (Meeting Abstracts). 2008;19 (Suppl 8):691PD.
8. Brose MS, Troxel AB, Harlacker K, Redlinger M, Chalian AA, Loevner LA, et al. Completion of a phase II study of sorafenib for advanced thyroid cancer [abstract]. Eur J Cancer Suppl (Meeting Abstracts). 2009;7:51LBA.
9. Kloos RT, Ringel MD, Knopp MV, Hall NC, King M, Stevens R, et al. Phase II trial of sorafenib in metastatic thyroid cancer. J Clin Oncol. 2009;27: 1675–84.
10. Gupta-Abramson V, Troxel AB, Nellore A, Puttaswamy K, Redlinger M, Ransone K, et al. Phase II trial of sorafenib in advanced thyroid cancer. J Clin Oncol. 2008;26:4714–9.
11. Brose MS, Nutting CM, Sherman SI, Shong YK, Smit JW, Reike G, et al. Rationale and design of decision: a double-blind, randomized, placebo-controlled phase III trial evaluating the efficacy and safety of sorafenib in patients with locally advanced or metastatic radioactive iodine (RAI)-refractory, differentiated thyroid cancer. BMC Cancer. 2011;11:349.
12. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: The phase III DECISION trial [abstract]. J Clin Oncol (Meeting Abstracts). 2013;31:4.
13. Baselga J, Schwartzberg LS, Petrenciuc O, Shan M, Gradishar WJ. Design of RESILIENCE: a phase (Ph) III trial comparing capecitabine (CAP) in combination with sorafenib (SOR) or placebo (PL) for treatment (tx) of locally advanced (adv) or metastatic HER2-negative breast cancer (BC) [abstract]. J Clin Oncol (Meeting Abstracts). 2011;29:TPS124.
14. Marrero J, Lencioni R, Ye SL, Kudo M, Bronowicki JP, Chen XP, et al. Final analysis of GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma [HCC] and of its treatment with sorafenib [Sor]) in >3000 Sor-treated patients (pts): clinical findings in pts with liver dysfunction [abstract]. J Clin Oncol. 2013;31:4126.
15. Zhang L, Zhou Q, Ma L, Wu Z, Wang Y. Meta-analysis of dermatological toxicities associated with sorafenib. Clin Exp Dermatol. 2011;36:344–50.
16. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Hepatobiliary Cancer. Version 2.2013. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site. Accessed January 22, 2014.
17. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Kidney Cancer. Version 2.2014. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site. Accessed January 22, 2014.

18. Porta C, Paglino C, Imarisio I, Bonomi L. Uncovering Pandora's vase: the growing problem of new toxicities from novel anticancer agents. The case of sorafenib and sunitinib. Clin Exp Med. 2007;7:127–34.
19. Ren Z, Zhu K, Kang H, Lu M, Qu Z, Lu L, 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 [abstract]. J Clin Oncol (Meeting Abstracts). 2012;30:4008.
20. Anderson R, Jatoi A, Robert C, Wood LS, Keating KN, Lacouture ME. Search for evidence-based approaches for the prevention and palliation of hand-foot skin reaction (HFSR) caused by the multikinase inhibitors (MKIs). Oncologist. 2009;14:291–302.
21. Autier J, Escudier B, Wechsler J, Spatz A, Robert C. Prospective study of the cutaneous adverse effects of sorafenib, a novel multikinase inhibitor. Arch Dermatol. 2008;144:886–92.
22. Frenette CT, Frederick RT, Gish RG. Clinical management and case reports for the treatment of hepatocellular carcinoma with sorafenib. J Clin Gastroenterol. 2011;45:733–7.
23. Lacouture ME, Reilly LM, Gerami P, Guitart J. Hand foot skin reaction in cancer patients treated with the multikinase inhibitors sorafenib and sunitinib. Ann Oncol. 2008;19:1955–61.
24. 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.
25. Flaherty KT, Brose MS. Sorafenib-related hand-foot skin reaction improves, not worsens, with continued treatment. Clin Cancer Res. 2009;15:7749.
26. Hutson TE, Bellmunt J, Porta C, Szczylik C, Staehler M, Nadel A, et al. Long-term safety of sorafenib in advanced renal cell carcinoma: follow-up of patients from phase III TARGET. Eur J Cancer. 2010;46:2432–40.
27. Terry RD, Keefe SM, Grande CM, Zifchak L, Brose MS. Timing and severity of skin-related adverse events in a phase II trial of sorafenib (BAY43-9006) in patients with advanced thyroid cancer [abstract]. J Clin Oncol (Meeting Abstracts). 2013;31:e17009.
28. Lacouture ME, Wu S, Robert C, Atkins MB, Kong HH, Guitart J, et al. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. Oncologist. 2008;13:1001–11.
29. Wood LS. Managing the side effects of sorafenib and sunitinib. Comm Oncol. 2006;3:558–62.
30. Perez-Soler, Delord JP, Halpern A, Kelly K, Krueger J, Sureda BM, et al. HER1/EGFR inhibitor-associated rash: future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. Oncologist. 2005;10:345–56.
31. Benson AB 3rd, Ajani JA, Catalano RB, Engelking C, Kornblau SM, Martenson JA Jr, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol. 2004;22:2918–26.
32. National Cancer Institute. Nutrition in cancer care (PDQ): diarrhea. October 24, 2013. http://www.cancer.gov/cancertopics/pdq/supportivecare/nutrition/HealthProfessional/page4#Section_148. Accessed January 22, 2014.
33. Maroun JA, Anthony LB, Blais N, Burkes R, Dowden SD, Dranitsaris G, et al. Prevention and management of chemotherapy-induced diarrhea in patients with colorectal cancer: a consensus statement by the Canadian Working Group on Chemotherapy-Induced Diarrhea. Curr Oncol. 2007;14:13–20.
34. National Cancer Institute. Gastrointestinal complications (PDQ): diarrhea. September 10, 2013. http://www.cancer.gov/cancertopics/pdq/supportivecare/gastrointestinalcomplications/HealthProfessional/page5. Accessed January 22, 2014.
35. Bellmunt J, Eisen T, Fishman M, Quinn D. Experience with sorafenib and adverse event management. Crit Rev Oncol Hematol. 2011;78:24–32.
36. Wood LS, Manchen B. Sorafenib: a promising new targeted therapy for renal cell carcinoma. Clin J Oncol Nurs. 2007;11:649–56.
37. Carafate (sucralfate) suspension prescribing information. Bridgewater, NJ; Aptalis Pharma US, Inc; 2013.
38. Maton PN. Profile and assessment of GERD pharmacotherapy. Cleve Clin J Med. 2003;70(suppl 5):S51–70.
39. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108:308–28.
40. Blei AT, Córdoba J. Practice Parameters Committee of the American College of Gastroenterology. Hepatic encephalopathy. Am J Gastroenterol. 2001;96:1968–76.
41. Shun SC, Lai YH, Jing TT, Jeng C, Lee FY, Hu LS, et al. Fatigue patterns and correlates in male liver cancer patients receiving transcatheter hepatic arterial chemoembolization. Support Care Cancer. 2005;13:311–7.
42. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Cancer-related fatigue. Version 1.2014. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed January 22, 2014.
43. Shah A, Motiwala S, Brose MS, O'Dwyer PJ, Flaherty K, Keefe SM. Increase in blood pressure with sorafenib exposure: renal cell carcinoma (RCC) versus other solid tumors [abstract]. J Clin Oncol (Meeting Abstracts). 2013;31:e15564.
44. Papadakis MA, Fraser CL, Arieff AI. Hyponatraemia in patients with cirrhosis. Q J Med. 1990;76:675–88.
45. Schuppan D, Afdhal NH. Liver cirrhosis. Lancet. 2008;371:838–51.
46. Ratain MJ, Eisen T, Stadler WM, Flaherty KT, Kaye SB, Rosner GL, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2006;24:2505–12.
47. Choueiri TK, Schutz FA, Je Y, Rosenberg JE, Bellmunt J. Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. J Clin Oncol. 2010;28:2280–5.
48. Haas NB, Manola J, Ky B, Flaherty KT, Uzzo RG, Wood CG, et al. Cardiac safety analysis for a phase III trial of

sunitinib (SU) or sorafenib (SO) or placebo (PLC) in patients (pts) with resected renal cell carcinoma (RCC) [abstract]. J Clin Oncol (Meeting Abstracts). 2012;30:4500.
49. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 2004. http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.htm. Accessed January 22, 2014.
50. Qamar AA, Grace ND, Groszmann RJ, Garcia-Tsao G, Bosch J, Burroughs AK, et al. Platelet count is not a predictor of the presence or development of gastroesophageal varices in cirrhosis. Hepatology. 2008;47:153–9.
51. Coriat R, Gouya H, Mir O, Ropert S, Vignaux O, Chaussade S, et al. Reversible decrease of portal venous flow in cirrhotic patients: a positive side effect of sorafenib. PLoS One. 2011;6:e16978.
52. Bari K, Garcia-Tsao G. Treatment of portal hypertension. World J Gastroenterol. 2012;18:1166–75.
53. Dodd MJ, Dibble SL, Miaskowski C, MacPhail L, Greenspan D, Paul SM, et al. Randomized clinical trial of the effectiveness of 3 commonly used mouthwashes to treat chemotherapy-induced mucositis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;90:39–47.
54. Harris DJ, Eilers J, Harriman A, Cashavelly BJ, Maxwell C. Putting evidence into practice: evidence-based interventions for the management of oral mucositis. Clin J Oncol Nurs. 2008;12:141–52.