Seminars in Oncology 46 (2019) 57–64

Contents lists available at ScienceDirect

Seminars in Oncology

journal homepage: www.elsevier.com/locate/seminoncol

Managing the adverse events associated with lenvatinib therapy in radioiodine-refractory differentiated thyroid cancer

Maria E. Cabanillas[a,*], Shunji Takahashi[b]

[a] Department of Endocrine Neoplasia & Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[b] Department of Medical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

ARTICLE INFO

Article history:
Received 2 November 2018
Accepted 21 November 2018

Keywords:
Adverse event
Differentiated thyroid cancer
Lenvatinib
Side effect
Tyrosine kinase inhibitor

ABSTRACT

Lenvatinib is a multikinase inhibitor of vascular endothelial growth factor (VEGF) receptors 1–3, fibroblast growth factor receptors 1–4, RET, KIT, and platelet-derived growth factor receptor-α. Lenvatinib is approved as a monotherapy for the treatment of radioiodine-refractory differentiated thyroid cancer and in combination with everolimus for the second-line treatment of advanced renal cell carcinoma. Lenvatinib is also under investigation for the treatment of several malignancies including unresectable hepatocellular carcinoma. Although lenvatinib is associated with favorable efficacy, it is associated with adverse events (AEs) that the clinician will have to closely monitor for and proactively manage. Most of these AEs are known class effects of VEGF-targeted therapies, including hypertension, diarrhea, fatigue or asthenia, decreased appetite, and weight loss. This review summarizes the safety profile of lenvatinib and offers guidance for the management of both frequent and rare AEs. We discuss the potential mechanisms underlying these AEs and present practical recommendations for managing toxicities. The development of treatment plans that include prophylactic and therapeutic strategies for the management of lenvatinib-associated AEs has the potential to improve patient quality of life, optimize adherence, minimize the need for dose reductions, treatment interruptions, or discontinuations, and maximize patient outcomes.

Introduction

Differentiated thyroid cancer (DTC) is the most common type of thyroid cancer in the United States, making up over 90% of all thyroid carcinoma cases [1,2]. For most patients diagnosed with DTC, standard treatment is surgery followed by administration of radioactive iodine [3,4]. However, a small percentage (10%–15%) of patients are either radioiodine insensitive or become refractory to radioiodine therapy, referred to as radioiodine-refractory DTC (RR-DTC) [1,2]. RR-DTC that has progressed has a poor prognosis, with most patients expected to live 3–6 years, and 90% of patients not surviving 10 years from the time of detection of metastasis [2,5,6]. Additional treatment options for patients with RR-DTC are therefore of particular interest [2] and a number of novel systemic therapies have come onto the market in recent years.

One of the newest classes of agent to demonstrate promising results in RR-DTC is tyrosine kinase inhibitor (TKI) therapy [2,7]. The first TKI to demonstrate a benefit in progression-free survival (PFS) in patients with RR-DTC was sorafenib, which was approved for the indication in 2013 by the US Food and Drug Administration [8,9]. More recently, lenvatinib has been approved for the treatment of locally recurrent or metastatic, progressive RR-DTC [4,10]. Lenvatinib is an oral multikinase inhibitor that acts on vascular endothelial growth factor (VEGF) receptors (VEGFR) 1–3, fibroblast growth factor (FGF) receptors (FGFR) 1–4, platelet-derived growth factor receptor-α (PDGFRα), and RET and KIT proto-oncogenes [11-15]. Preclinical studies of lenvatinib activity showed that it decreased angiogenesis, and in xenograft models of cancer lenvatinib demonstrated potent antitumor activity [11,15,16]. Lenvatinib targets FGFR in addition to VEGFR, which may help prevent the development of resistance to TKI therapies, as the FGFR pathway is known to provide an escape pathway in tumor cells being targeted by VEGFR inhibitors [17]. Lenvatinib demonstrated significantly prolonged PFS versus placebo (median PFS 18.3 *v* 3.6 months; hazard ratio [HR], 0.21; 99% confidence interval [CI], 0.14–0.31; $P < .001$) in the phase 3 Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) [18]. The response rate with lenvatinib treatment was also significantly higher than for placebo (65% *v* 1.5%; $P < .001$) [18].

* Corresponding author. Department of Endocrine Neoplasia and Hormonal Disorders, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, PO Box 301402, Unit 1461, Houston, TX 77230-1402, USA.
E-mail address: mcabani@mdanderson.org (M.E. Cabanillas).

https://doi.org/10.1053/j.seminoncol.2018.11.004

With the approval of sorafenib and lenvatinib (in addition to other TKIs for various indications), the use of kinase inhibitors in the clinic has become increasingly common. As TKIs are generally used as chronic therapies, it is important to effectively manage and minimize the toxicities that may be experienced by patients, enabling them to remain on treatment for as long as the therapies provide benefit [19]. This review will focus on the toxicities associated with lenvatinib in patients receiving it as monotherapy for RR-DTC.

Toxicity profile of lenvatinib in radioiodine-refractory differentiated thyroid cancer

Most patients (97.3%) in SELECT who received lenvatinib reported adverse events (AEs) during the study compared with 59.5% of the patients receiving placebo [18]. Three-quarters of the patients receiving lenvatinib experienced treatment-related AEs of grade 3 or higher severity in this study, highlighting the need for careful management of the toxicities associated with this therapy to maximize benefits for patients. The most common AEs associated with lenvatinib in SELECT were hypertension (67.8%), diarrhea (59.4%), fatigue or asthenia (59.0%), decreased appetite (50.2%), decreased weight (46.4%), nausea (41.0%), stomatitis (35.6%), palmar-plantar erythrodysesthesia syndrome (PPES; 31.8%), and proteinuria (31.0%) [18]. These common AEs associated with lenvatinib are typical of the AEs reported more generally with TKIs in patients with thyroid cancer [19].

Interruptions to lenvatinib treatment may compromise the efficacy gains that the patient could experience. In the pivotal SELECT, discontinuation of treatment due to AEs occurred in 14.2% of patients who received lenvatinib compared with 2.3% patients who received placebo [18]. The AEs most commonly associated with treatment withdrawal were asthenia and hypertension. Dose interruptions and reductions were, as expected, more common in the lenvatinib group than in the placebo group (interruptions: 82.4% *v* 18.3%; reductions: 67.8% *v* 4.6%, respectively) [18]. Lenvatinib dose modifications were most commonly implemented to manage diarrhea (22.6%), hypertension (19.9%), proteinuria (18.8%), and decreased appetite (18.0%) [18].

A further analysis of SELECT showed that older patients tended to experience higher toxicity from lenvatinib treatment compared with younger counterparts [20]. In particular, more patients in the older group (>65 years) experienced AEs of grade 3 or higher during lenvatinib treatment than patients in the younger group (88.7% *v* 67.1%, respectively), and older patients were more likely to require dose interruptions and reductions or to discontinue therapy [20]. Of note, an analysis of the timing of the onset of common AEs in SELECT (diarrhea, fatigue/asthenia/malaise, proteinuria, and PPES) concluded that these AEs typically occurred quite early after treatment initiation (within the first 2 months), with incidence diminishing over the course of treatment [21]. The authors of this analysis posited that although this observation may be due to a reporting bias by patients who eventually become inured to such AEs, it is also possible that symptoms may improve over time for at least some of these AEs [21].

Management of adverse events

Most of the toxicities commonly associated with lenvatinib therapy in patients with RR-DTC are shared by other multikinase inhibitors [18,19,22,23]. Inadequate management of AEs associated with TKI therapy may result in poor adherence and early discontinuation from treatment, as one study of TKI treatment in patients with advanced thyroid cancer has reported [24]. The strategies for managing AEs in the clinic include supportive care, dose modifications, and, if necessary, discontinuation of lenvatinib therapy. Thorough patient education about the signs and symptoms of the AEs that may occur when lenvatinib treatment commences, and early clinical intervention when AEs are reported, can improve the likelihood of efficacy and maintenance of quality of life throughout treatment with lenvatinib [25]. AEs associated with lenvatinib therapy that may occur in clinical practice are listed in Table 1, along with their Common Terminology Criteria for Adverse Events grading descriptions and proposed management strategies.

Hypertension

Multikinase inhibition has been associated with development of hypertension in clinical trials [26,27]. Most studies with lenvatinib have reported high incidences of hypertension, including in RR-DTC [18,28] and in renal cell carcinoma in combination with everolimus [29-31]. In SELECT, hypertension occurred in approximately 68% of patients receiving lenvatinib, and was of grade 3 or greater severity in over 40% [18]. The median time to development of hypertension was 2.3 weeks (range: 1.4–5.0) in this study [32].

In the Japanese population of SELECT, hypertension occurred more frequently (any-grade, 87%; grade ≥3, 80%) [33]. Treating the symptoms remains the focus of clinical intervention because the underlying cause of hypertension during TKI therapy is not yet well understood [34]. Recently published evidence indicates that lenvatinib-induced hypertension may be caused by lowered nitric oxide production because of VEGF inhibition and impaired vascular endothelial function [35]. It has been suggested that development of drug-induced hypertension in patients receiving antiangiogenic therapies may correlate with on-target activity of the agent [36]; correspondingly, an association between lenvatinib-emergent hypertension and PFS has been reported [32].

Diagnosing hypertension early may help avoid serious complications and allow patients to stay on treatment [37,38]. The use of 24-hour blood pressure (BP) monitoring may provide early detection and accurate assessment of BP changes. Twenty-four-hour BP monitoring has detected the early development of hypertension in patients receiving a TKI [38]. Patients regularly monitoring their BP at home during sunitinib therapy were able to detect early changes in BP that might be missed during sporadic office visits [37]. For optimal outcome, patients should be provided with individualized BP thresholds that may reflect any additional risk factors, and can serve as an indicator to their health care provider if earlier intervention is needed (even if technically the patient's BP was still within "normal" limits).

Once hypertension has developed, it should be managed with standard antihypertensive therapy. Published guidelines for treatment of hypertension suggest initiation of pharmacologic treatment when systolic BP is ≥140 mmHg or diastolic BP is >90 mmHg [39,40]. If medical therapy is required, standard options include calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), diuretics/thiazides, and β-adrenoceptor blockers [34]. Drugs can be administered as monotherapy or in combination, and titration to full dose strength can be done one drug at a time, or simultaneously if more than one drug is introduced at the same time [41]. Hypertension should be managed aggressively to avoid adverse outcomes.

Proteinuria

In SELECT, approximately one-third of patients receiving lenvatinib experienced proteinuria of any grade, and 10% had severe (grade ≥3) proteinuria [18]. In the Japanese population of SELECT, proteinuria occurred more frequently (any-grade, 63.3%; grade ≥3, 20%) [33]. Proteinuria is a recognized class effect of antiangiogenic therapy, first identified with the VEGF antibody bevacizumab, but common to most TKIs [19]. At baseline, all

Table 1
Common adverse events with lenvatinib and recommended management of lenvatinib dose and drug holds [10,25,43,81,82].

Adverse event	CTCAE grade	CTCAE description	Action
Hypertension	1	Asymptomatic, transient (<24 h) increase >20 mmHg (diastolic), or to >150/100 mmHg if previously within normal limits; intervention not indicated	• No lenvatinib dose change • Manage hypertension aggressively to keep blood pressure ≤140/90 mmHg
	2	Recurrent or persistent (<24 h) increase >20 mmHg (diastolic), or to >150/100 mmHg if previously within normal limits; monotherapy may be indicated	• No lenvatinib dose change unless antihypertensive treatments fail to control blood pressure • Manage hypertension aggressively to keep blood pressure ≤140/90 mmHg
	3	Requiring >1 drug or more intensive therapy than previously	• Hold lenvatinib until hypertension resolves to grade ≤2 • Manage hypertension aggressively to keep blood pressure ≤140/90 mmHg
	4	Life-threatening	• Discontinue lenvatinib permanently • Treat blood pressure with intensive intravenous fluid support in the intensive care unit
Proteinuria	1	0.15–1.0 g/24 h	• None
	2	>1.0–3.5 g/24 h	• Hold lenvatinib until proteinuria resolves to ≤2.0 g/24 h • Consider referral to Nephrology
	3	>3.5 g/24 h	• Hold lenvatinib until proteinuria resolves to ≤2.0 g/24 h • Refer patient to Nephrology
	4	Nephrotic syndrome	• Discontinue lenvatinib permanently
Fatigue/asthenia	1	Mild fatigue over baseline	• None; discuss supportive strategies with patients • Check thyroid-stimulating hormone and hemoglobin levels
	2	Moderate fatigue, or causing difficulty performing some activities of daily living	• Discuss coping strategies with patients • Check thyroid-stimulating hormone and hemoglobin levels
	3	Severe fatigue interfering with activities of daily living	• Consider dose interruption • Check thyroid-stimulating hormone and hemoglobin levels
	4	Disabling	• Discontinue lenvatinib if no improvement • Check thyroid-stimulating hormone and hemoglobin levels
Nausea	1	Loss of appetite; oral intake same	• No lenvatinib dose change; symptomatic management
	2	Oral intake reduced without weight loss, dehydration or malnutrition; intravenous fluids <24 h	• No lenvatinib dose change; symptomatic management
	3	Inadequate oral caloric or fluid intake; intravenous fluids, tube feeding, or total parenteral nutrition for ≥24 h	• Hold lenvatinib until nausea resolves to grade ≤1
	4	Life-threatening consequences	• Hold lenvatinib until nausea resolves to grade ≤1
Diarrhea	1	+ <4 stools/d; mild increase in ostomy output	• No lenvatinib dose change • Educate patient on over-the-counter medications to manage diarrhea (eg, loperamide)
	2	+ 4–6 stools/d; moderate increase in ostomy output; no interference with activities of daily living; intravenous fluids <24 h	• No lenvatinib dose change • Ensure compliance with over-the-counter antidiarrhea medication and consider prescription medication treatment options for diarrhea
	3	+ ≥7 stools/d; severe increase in ostomy output; interference with activities of daily living; hospitalization; intravenous fluids ≥24 h	• Hold lenvatinib until diarrhea resolves to grade ≤1 • See management of grade 2 diarrhea (above)
	4	Life-threatening consequences	• Discontinue lenvatinib permanently
Vomiting	1	1 event per 24 h	• No lenvatinib dose change • Monitor and educate patient on taking lenvatinib with food
	2	2–5 events per 24 h; intravenous fluids <24 h	• No lenvatinib dose change • Symptomatic management of nausea and vomiting • Educate patient on taking lenvatinib with food
	3	≥6 events per 24 h; intravenous fluids, or total parenteral nutrition indicated ≥24 h	• Hold lenvatinib until vomiting resolves to grade ≤1 • Symptomatic management of nausea, vomiting, and possible dehydration
	4	Life-threatening consequences	• Discontinue lenvatinib permanently • See management of grade 3 vomiting (above)
Stomatitis	1	Erythema of the mucosa; minimal symptoms; normal diet	• No lenvatinib dose change • Advise patient to avoid foods and toothpastes that exacerbate stomatitis
	2	Patchy ulcerations; symptomatic but can eat and swallow modified diet	• Topical analgesics for pain and corticosteroids for inflammation • Continue lenvatinib
	3	Confluent ulcerations; bleeding with minor trauma; symptomatic with inadequate oral intake	• Hold lenvatinib until stomatitis grade ≤2
	4	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	• Discontinue lenvatinib
Palmar-plantar erythrodysesthesia	1	Minimal skin changes or dermatitis (eg, erythema) without pain	• Continue lenvatinib • Apply moisturizer or other topical lotions as required (see Fig. 1) • Dermatology and/or podiatry consult for early intervention may be considered
	2	Skin changes (eg, peeling, blisters, bleeding, edema) or pain, not interfering with function	• Consider topical corticosteroids or urea creams (see Fig. 1) • Consider dermatology and/or podiatry consult
	3	Ulcerative dermatitis or skin changes with pain interfering with function	• Hold lenvatinib until palmar-plantar erythrodysesthesia resolves to grade ≤1 • See Fig. 1

patients who will receive lenvatinib should have a urinalysis and protein:creatinine ratio measured, and should undergo routine testing for the development of proteinuria throughout treatment [19]. The decision to interrupt lenvatinib treatment or modify the dose should be considered on a case-by-case basis; importantly, switching a patient to another antiangiogenic TKI may not be of any benefit because proteinuria is a class effect of antiangiogenic treatments [19].

Fatigue/asthenia

Fatigue can arise as a symptom of the underlying cancer, as an AE of lenvatinib, and/or as a sign of hypothyroidism, anemia, depression, sleep disturbances, or pain. For example, fatigue can be caused by a rise in thyroid-stimulating hormone levels. In SELECT, 57% of patients treated with lenvatinib experienced thyroid-stimulating hormone levels above 0.5 mU/L, compared with 14% of patients on placebo [10]. Fatigue affects patients as a distressing and persistent sense of emotional, physical, and/or cognitive tiredness or exhaustion. Cancer-related fatigue is common, occurring in approximately three-quarters of patients with metastatic disease, and can significantly adversely affect a patient's quality of life [42].

Managing fatigue can be difficult. The initial step is to identify any treatable cause, if one exists (eg, anemia, thyroid dysfunction, poor sleep, or depression) [43]. Thyroid function should be tested prior to initiation of lenvatinib treatment and then monitored monthly, with adjustment of any thyroid-replacement medication as necessary. If no underlying etiology can be identified, treatment for fatigue includes supportive care with adequate nutrition, exercise, and the implementation of stress-reducing techniques [19]. However, exercise is not recommended for lenvatinib-treated patients experiencing PPES because this AE is exacerbated by exercise. The physician should also consider lenvatinib dose interruption if a patient complains of moderate to severe fatigue.

Diarrhea/nausea/other gastrointestinal adverse events

Diarrhea was a very common AE in SELECT, experienced by two-thirds of the patients in the lenvatinib study arm. Nausea and vomiting were also relatively common (41% and 28%, respectively) [18]. Gastrointestinal AEs were also commonly experienced with lenvatinib in clinical practice (diarrhea, 45%; nausea, 18%) [44]. A recent (2017) meta-analysis of phase 2 and 3 clinical trials showed that gastrointestinal AEs are a common class side effect of VEGFR-TKIs [45]. Diarrhea, in particular, can be life-threatening if not managed adequately [43].

Published guidelines for managing diarrhea associated with cancer or chemotherapy suggest that patient education is important, and patients should keep diaries listing episodes and severity, and any accompanying symptoms. Management strategies include diet modification (avoidance of foods that may aggravate diarrhea and consuming foods that may increase stool consistency), dehydration management, therapeutic interventions such as loperamide, and dose adjustments for patients who experience grade 3 or 4 AEs. First-line therapeutic interventions are typically loperamide or diphenoxylate/atropine; budesonide or tincture of opium may also be used. Referral to a gastroenterologist may be indicated to rule out exacerbation of an underlying cause of diarrhea, such as ulcerative colitis. Optimal treatment dosing may be resumed once severe diarrhea has subsided.

Stomatitis/mucositis

Stomatitis or mucositis occurs often in patients receiving TKIs and other targeted therapies [43]. Stomatitis is a painful inflammation of the mucous lining of the mouth, whereas mucositis refers to inflammation or ulceration of the mucous membranes lining the digestive tract; both AEs can make it difficult to speak, eat, or even open the mouth [43]. In patients with RR-DTC treated with lenvatinib, stomatitis was a relatively common AE, occurring in 20%–36% of patients in clinical trials [18,28] and in approximately 1 in 4 patients treated with lenvatinib in a real-world study [44]. Most cases of stomatitis were of mild or moderate severity (grade $\leq$2) and did not usually necessitate withdrawal of lenvatinib treatment [18,28,44].

Patient awareness and early intervention are important to minimize discomfort for the patient and improve adherence to therapy for maximum clinical benefit. Patients should be warned to avoid mint-flavored toothpaste, alcohol-containing mouthwash, and spicy or acidic foods, which can exacerbate stomatitis. Treatment for stomatitis occurring in patients receiving lenvatinib is similar to that recommended for patients receiving other targeted antiangiogenic agents [46-48]. Good oral hygiene is the first prophylactic measure, and patients should brush their teeth after each meal and then rinse with salt-water and baking soda mouthwash solutions (1/2 teaspoon baking soda in 8 ounces of water) to help with that process. Currently, clinical trials evaluating the efficacy of steroid mouthwash in patients with stomatitis are underway and can potentially reduce the incidence, severity, and duration of stomatitis in patients receiving lenvatinib [49,50]. Additional oral care recommendations include scheduling a dental visit prior to treatment with lenvatinib as well as the use of a soft toothbrush and fluoride toothpaste without tartar or whitening control during treatment. Topical lidocaine or steroid ointment may also be helpful for painful ulcerations, although for more severe stomatitis (grade $\geq$3) dose reductions or interruptions may be necessary [46-48].

Palmar-plantar erythrodysesthesia syndrome

PPES is another AE that is common across TKI therapies, and was common in clinical trials of lenvatinib in RR-DTC [18,28]. In the Japanese population of SELECT, PPES also occurred more frequently (70%; grade $\geq$3, 3%) compared with the total population (32%; grade $\geq$3, 3%), but severe cases are rare [33]. The management strategies used for managing PPES in patients receiving TKIs for other cancers are also applicable to lenvatinib-associated PPES in RR-DTC, and range from preventative measures to topical medication once it has developed [51,52]. Prophylaxis may include pretreatment examination of the soles of the feet and palms and removal of any existing hyperkeratotic areas and calluses present, which can then be protected by cushioning and treated with moisturizing creams and keratolytic agents [52]. Patients should be educated about the visible signs of PPES to help with the early detection of symptoms [51]. During treatment, patients should be encouraged to reduce exposure of the hands and feet to hot water, avoid tight footwear, and limit damage caused by vigorous exercise. As most patients develop PPES within the first 2–4 weeks of initiating TKI therapy, avoiding traumatic activity and sufficient rest during this time may be important [52]. A suggested treatment algorithm for PPES is outlined in Fig. 1. Finally, PPES management can require dose reduction or interruption of lenvatinib treatment until the AE has resolved back to grade $\leq$1 severity [52]. It may also be appropriate to consult with a dermatologist and/or podiatrist for patients experiencing persistent grade 2 or grade 3 PPES.

Hemorrhagic events

Antiangiogenic therapies are associated with an increased risk of hemorrhagic complications [53,54]. In SELECT, 35% of

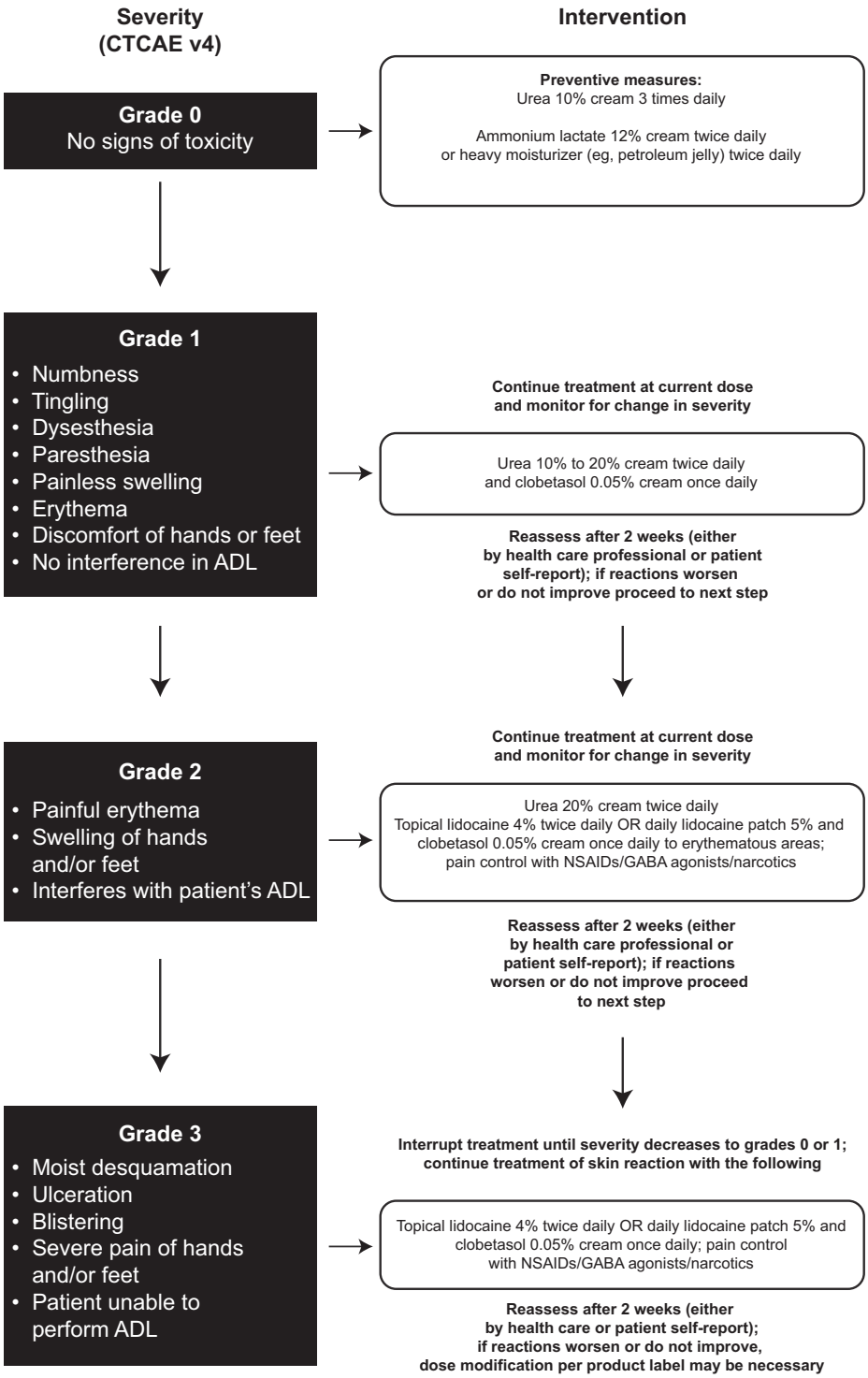

Fig. 1. Treatment algorithm for palmar-plantar erythrodysesthesia [51,52]. Abbreviations: ADL, activities of daily living; CTCAE, Common Terminology Criteria for Adverse Events; GABA, gamma-aminobutyric acid; NSAIDs, nonsteroidal anti-inflammatory drugs. Adapted with permission from Lacouture et al. *Thyroid*. 2014;24:1329-1340, ©Mary Ann Liebert, Inc., [51]; and Lacouture et al. *The Oncologist*. 2008;13:1001-1011, ©AlphaMed Press [52].

lenvatinib-treated patients experienced hemorrhagic events compared with 18% of the placebo group [10]. Possible mechanisms for the increased incidence of hemorrhagic complications for patients treated with lenvatinib include blood vessel destabilization due to decreased matrix deposition, loss of vascular integrity resulting in blood vessel rupture, and thrombocytopenia [19,54]. Patients who are taking blood thinners, who have undergone previous bowel surgery, or have a history of inflammatory bowel disease or diverticulitis, are at further increased risk for bowel perforation and gastrointestinal bleeding. Lenvatinib should be withheld in patients who develop a grade 3 hemorrhage until resolved to grade 0 or 1 [10]. Once resolved, lenvatinib can be resumed at a reduced dose or discontinued depending on the severity of the hemorrhagic event. Lenvatinib should be discontinued in patients who experience a grade 4 hemorrhagic event [10].

Wound healing

Antiangiogenic TKIs are associated with wound healing complications [19,53-55]. As angiogenesis is required for the maintenance of vascular integrity, epithelialization, and wound strength, inhibition of this process can delay or impair wound repair, particularly after surgery [19,53,54,56,57]. Consequently, clinical trials with antiangiogenic therapies typically require temporary discontinuation of the drug before major surgery [53]. Therefore, lenvatinib should be withheld before and after surgery and should only be resumed upon adequate wound healing. It is unclear how long lenvatinib should be held prior to surgery, but in the authors' practice, a drug hiatus of 3–5 half-lives, depending on the extent of surgery, is usually warranted.

Thrombocytopenia

Thrombocytopenia is a serious complication associated with anti-VEGF TKIs [53,58]. In SELECT, thrombocytopenia occurred in 8.8% of lenvatinib-treated patients and was of grade 3 or worse severity in 1.5% [33]. In the Japanese population of SELECT, 46.7% of lenvatinib-treated patients experienced thrombocytopenia and 6.7% of patients experienced severe thrombocytopenia (grade $\geq$3) [33]. Additionally, a systematic meta-analysis of relevant clinical trials showed that thrombocytopenia was the most frequently observed grade 3 or worse treatment-related AE (25.4%) in patients receiving lenvatinib [58].

Lenvatinib-induced thrombocytopenia may be caused by the suppression of hematopoiesis due to the inhibition of PDGFR, a known target of lenvatinib [56,58-60]. Throughout the course of treatment, complete blood counts should be routinely monitored for evidence of thrombocytopenia [19,58]. Lenvatinib dose reductions upon the first or second occurrence are recommended for patients experiencing grade 3 or 4 thrombocytopenia [19].

Rare AEs

The following sections detail several rare but important AEs that have been associated with antiangiogenic TKIs.

Gastrointestinal perforation (GIP)/fistula formation

GIP or fistula formation is a rare but life-threatening AE associated with antiangiogenic TKIs [4,19,61,62]. In SELECT, fistula formation occurred in 1.5% of patients receiving lenvatinib, with 0.8% experiencing a grade 3 or worse event [18]. Risk factors for GIP include tumor at the perforation site, abdominal carcinomatosis, previous bowel surgery, bowel obstruction, intra-abdominal abscess, recent history of sigmoidoscopy or colonoscopy, and history of pelvic or abdominal irradiation [19,61,63]. Although the cause of GIP in antiangiogenic TKI-treated patients is unknown, studies show that VEGF inhibition results in the disturbance of platelet–endothelial cell interactions, which can lead to loss of vascular integrity and submucosal inflammation [56,63]. Antiangiogenic therapies may also contribute to the development of GIP via several additional mechanisms including exacerbation of existing ulcers or diverticulitis, tumor necrosis, and ischemic perforation of normal bowel or anastomosis [54].

Patients starting treatment with lenvatinib or other TKIs should be advised that if they experience abdominal pain or gastrointestinal bleeding, they should seek immediate medical attention [10]. The management of GIP includes total parenteral nutrition, bowel rest, intravenous fluids, broad-spectrum antibiotics, nasogastric tube placement, and percutaneous intraperitoneal catheter placement [54,64,65]. It is important to note that surgical intervention can be complicated by impaired wound healing in patients treated with antiangiogenic therapies [54]. Lenvatinib-treated patients who develop GIP or fistulas should discontinue therapy [10].

Tracheoesophageal fistula formation (TEF)

TEF formation is a rare complication of antiangiogenic therapy [66,67]. Risk factors for TEF formation include tumor extension into the mediastinum and tracheoesophageal injury due to esophagitis, esophageal or airway instrumentation (eg, endotracheal intubation, bronchoscopy, and endoscopy), and local treatment (eg, external beam radiation, surgery, and bronchial artery embolization) [66,67]. Because antiangiogenic therapies can impair or delay wound healing, the administration of antiangiogenic TKIs in patients with pre-existing risk factors may play a role in the development of TEFs. In SELECT, no patients receiving lenvatinib experienced a TEF [18]. However, should a patient receiving lenvatinib develop TEF, lenvatinib treatment should be discontinued as TEF formation can be fatal.

Reversible posterior leukoencephalopathy syndrome (RPLS)

RPLS is a neurologic disorder characterized by severe headache, seizures, confusion, or visual disturbances, and it is often associated with severe hypertension [68-70]. Strict and meticulous attention to BP control may help to prevent this AE [70-72]. In SELECT, RPLS occurred in 0.4% of patients receiving lenvatinib [18]. The key anatomic pathologic finding in patients with RPLS is posterior subcortical vasogenic edema [73,74]. As clinical findings are not specific enough to diagnose RPLS, the diagnosis needs to be confirmed by magnetic resonance imaging [10,75]. Discontinuation of lenvatinib is recommended until RPLS has been fully resolved [10]. Once resolved, lenvatinib treatment can be resumed at a reduced dose or permanently discontinued, depending on the severity of neurologic impairment [10].

Congestive heart failure (CHF)

CHF is an uncommon but serious AE that has been observed in patients treated with TKIs [10,19,76]. The inhibition of VEGFR or PDGFR may cause cardiomyocyte cell death and prevent cardiac remodeling, resulting in cardiac dysfunction [77,78]. In SELECT, 7% of patients treated with lenvatinib experienced cardiac dysfunction (ie, decreased left or right ventricular function, cardiac failure, or pulmonary edema) and 2% of lenvatinib-treated patients experienced severe (grade $\geq$3) cardiac dysfunction [10]. The increased risk of hypertension due to lenvatinib treatment may also play a role in the increased incidence of cardiac disease.

A baseline echocardiogram is recommended prior to the initiation of TKI therapy and periodically throughout the course of treatment [19]. Careful monitoring and administration of routine heart failure therapies (eg, beta blockers and ACEi/ARB) are recommended for the management of heart failure [10,19]. Diuretics can also be administered to assist with fluid overload and edema [79,80]. Lenvatinib should be withheld for grade 3 cardiac dysfunction until resolution to grade 0 or 1. Upon resolution, lenvatinib can be resumed at a lower dose or discontinued depending on disease severity [10]. If lenvatinib is resumed, BP should be monitored daily and maintained within the normal range. Lenvatinib should be discontinued for grade 4 cardiac dysfunction [10].

Thrombotic events

An increased risk for thrombotic events is associated with antiangiogenic therapies [54]. In SELECT, arterial thromboembolic events (ATEs) occurred in 5.4% of lenvatinib-treated patients, and 2.7% of patients had severe (grade $\geq$3) ATEs [18]. Similarly, 5.4% of patients treated with lenvatinib experienced venous thromboembolic events (VTEs), with 3.8% of patients experiencing grade $\geq$3

Table 2
Relative contraindications to potent antiangiogenic drugs. These relative contraindications should prompt a discussion with the patient regarding the risks and possibly a lower starting dose or alternate drug choice.[a]

Relative contraindications to potent antiangiogenic agents
• Poor cardiac function or recent myocardial infarction
• Uncontrolled hypertension
• Large, unhealed wounds
• History of colitis, diverticulitis, intestinal perforation, recent bowel surgery
• Tumor invading trachea/esophagus/great vessels
• Hemoptysis or use of anticoagulants
• Very low body weight (body mass index: 18–21 kg/m^2)

[a] These recommendations are based on the author's clinical experience.

VTEs [18]. One lenvatinib-related death due to pulmonary embolism occurred in SELECT [18]. The increased incidence of thrombotic events with antiangiogenic therapies may be due to VEGF inhibition, which can result in the overproduction of erythropoietin and subsequent increases in hematocrit and blood viscosity [19]. Lenvatinib should be discontinued and the appropriate antiplatelet or anticoagulation regimen should be initiated following a thromboembolic event [10,80].

Treating patients with relative contraindications

Table 2 lists the relative contraindications to potent antiangiogenic drugs. Patients with other comorbidities or low body weight may find it challenging to start lenvatinib therapy on a full dose or even a reduced dose. In those cases, a nonantiangiogenic alternative could be considered. Although surgical hypoparathyroidism is not a relative contraindication, these patients are at risk of hypocalcemia when receiving lenvatinib and, therefore, frequent monitoring of calcium levels is warranted. For patients with severe renal or hepatic impairment and DTC, the approved starting dose of lenvatinib is 14 mg once daily instead of 24 mg once daily [10]. A phase 2 clinical trial (ClinicalTrials.gov NCT02702388) is underway to investigate if a lower lenvatinib starting dose of 18 mg will yield comparable efficacy to the 24-mg dose in patients with RR-DTC (with an improved safety profile).

Conclusions

The toxicity pattern associated with lenvatinib therapy in patients with RR-DTC is highly predictable and similar to that of many other multikinase inhibitors. Comprehensive patient education to increase awareness of signs and symptoms of possible AEs and proactive patient monitoring can result in early detection and management before AEs become too severe. Careful and appropriate management of AEs will increase the likelihood of patients remaining on full doses of lenvatinib in order to receive maximal benefit from treatment.

Conflicts of interest

Maria E. Cabanillas: Reports personal fees from LOXO, Blueprint, and Ignyta; and research grants from Eisai, Exelixis, Genentech, and Kura.

Shunji Takahashi: Reports research grants and personal fees from Eisai, Bayer, Novartis, Taiho, MSD, Chugai, AstraZeneca, and Daiichi-Sankyo.

Funding

This work was supported by Eisai Inc., New Jersey, USA, and involved funding of editorial support for Oxford PharmaGenesis Inc., Newtown, PA, USA.

Acknowledgments

Editorial support was provided by Irene Ojini, PhD of Oxford PharmaGenesis Inc., Newtown, PA, USA.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.seminoncol.2018.11.004.

References

[1] Busaidy NL, Cabanillas ME. Differentiated thyroid cancer: management of patients with radioiodine nonresponsive disease. J Thyroid Res 2012;2012:618985.
[2] Pacini F, Ito Y, Luster M, et al. Radioactive iodine-refractory differentiated thyroid cancer: unmet needs and future directions. Expert Rev Endocrinol Metab 2012;7:541–54.
[3] Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–214.
[4] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Thyroid carcinoma. Version 1; 2018 https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf [Accessed October 3, 2018].
[5] Durante C, Haddy N, Baudin E, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab 2006;91:2892–9.
[6] Xing M, Haugen BR, Schlumberger M. Progress in molecular-based management of differentiated thyroid cancer. Lancet 2013;381:1058–69.
[7] Gruber JJ, Colevas AD. Differentiated thyroid cancer: focus on emerging treatments for radioactive iodine-refractory patients. Oncologist 2015;20:113–26.
[8] Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 2014;384:319–28.
[9] Worden F. Treatment strategies for radioactive iodine-refractory differentiated thyroid cancer. Ther Adv Med Oncol 2014;6:267–79.
[10] Eisai Inc. Lenvima (lenvatinib) [prescribing information]. Eisai Inc., Woodcliff Lake, NJ, 2017.
[11] Matsui J, Funahashi Y, Uenaka T, et al. Multi-kinase inhibitor E7080 suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 via inhibition of vascular endothelial growth factor-receptor (VEGF-R) 2 and VEGF-R3 kinase. Clin Cancer Res 2008;14:5459–65.
[12] Matsui J, Yamamoto Y, Funahashi Y, et al. E7080, a novel inhibitor that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition. Int J Cancer 2008;122:664–71.
[13] Okamoto K, Kodama K, Takase K, et al. Antitumor activities of the targeted multi-tyrosine kinase inhibitor lenvatinib (E7080) against RET gene fusion–driven tumor models. Cancer Lett 2013;340:97–103.
[14] Tohyama O, Matsui J, Kodama K, et al. Antitumor activity of lenvatinib (e7080): an angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. J Thyroid Res 2014;2014:638747.
[15] Yamamoto Y, Matsui J, Matsushima T, et al. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. Vasc Cell 2014;6:18.
[16] Ikuta K, Yano S, Trung VT, et al. E7080, a multi-tyrosine kinase inhibitor, suppresses the progression of malignant pleural mesothelioma with different proangiogenic cytokine production profiles. Clin Cancer Res 2009;15:7229–37.
[17] Laursen R, Wehland M, Kopp S, et al. Effects and role of multikinase inhibitors in thyroid cancer. Curr Pharm Des 2016;22:5915–26.
[18] Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 2015;372:621–30.
[19] Cabanillas ME, Hu MI, Durand JB, Busaidy NL. Challenges associated with tyrosine kinase inhibitor therapy for metastatic thyroid cancer. J Thyroid Res 2011;2011:985780.
[20] Brose MS, Worden FP, Newbold KL, Guo M, Hurria A. Effect of age on the efficacy and safety of lenvatinib in radioiodine-refractory differentiated thyroid cancer in the phase III SELECT trial. J Clin Oncol 2017;35:2692–9.
[21] Haddad RI, Schlumberger M, Wirth LJ, et al. Incidence and timing of common adverse events in Lenvatinib-treated patients from the SELECT trial and their association with survival outcomes. Endocrine 2017;56:121–8.
[22] Brose MS, Frenette CT, Keefe SM, Stein SM. Management of sorafenib-related adverse events: a clinician's perspective. Semin Oncol 2014;41(suppl 2):S1–S16.
[23] Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol 2013;31:3639–46.
[24] Chrisoulidou A, Mandanas S, Margaritidou E, et al. Treatment compliance and severe adverse events limit the use of tyrosine kinase inhibitors in refractory thyroid cancer. Onco Targets Ther 2015;8:2435–42.

[25] Jasim S, Iniguez-Ariza NM, Hilger CR, et al. Optimizing lenvatinib therapy in patients with metastatic radioactive iodine-resistant differentiated thyroid cancers. Endocr Pract 2017;23:1254–61.
[26] Small HY, Montezano AC, Rios FJ, Savoia C, Touyz RM. Hypertension due to antiangiogenic cancer therapy with vascular endothelial growth factor inhibitors: understanding and managing a new syndrome. Can J Cardiol 2014;30:534–543.
[27] Wasserstrum Y, Kornowski R, Raanani P, et al. Hypertension in cancer patients treated with anti-angiogenic based regimens. Cardiooncology 2015;1:6.
[28] Schlumberger M, Jarzab B, Cabanillas ME, et al. A phase II trial of the multitargeted tyrosine kinase inhibitor lenvatinib (E7080) in advanced medullary thyroid cancer. Clin Cancer Res 2016;22:44–53.
[29] Bendtsen MAF, Grimm D, Bauer J, et al. Hypertension caused by lenvatinib and everolimus in the treatment of metastatic renal cell carcinoma. Int J Mol Sci 2017;18:E1736. doi:10.3390/ijms18081736.
[30] Molina AM, Hutson TE, Larkin J, et al. A phase 1b clinical trial of the multi-targeted tyrosine kinase inhibitor lenvatinib (E7080) in combination with everolimus for treatment of metastatic renal cell carcinoma (RCC). Cancer Chemother Pharmacol 2014;73:181–9.
[31] Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol 2015;16:1473–82.
[32] Wirth LJ, Tahara M, Robinson B, et al. Treatment-emergent hypertension and efficacy in the phase 3 Study of (E7080) lenvatinib in differentiated cancer of the thyroid (SELECT). Cancer 2018;124:2365–72.
[33] Kiyota N, Schlumberger M, Muro K, et al. Subgroup analysis of Japanese patients in a phase 3 study of lenvatinib in radioiodine-refractory differentiated thyroid cancer. Cancer Sci 2015;106:1714–21.
[34] Ancker OV, Wehland M, Bauer J, Infanger M, Grimm D. The adverse effect of hypertension in the treatment of thyroid cancer with multi-kinase inhibitors. Int J Mol Sci 2017;18:E625. doi:10.3390/ijms18030625.
[35] Sueta D, Suyama K, Sueta A, et al. Lenvatinib, an oral multi-kinases inhibitor, -associated hypertension: Potential role of vascular endothelial dysfunction. Atherosclerosis 2017;260:116–20.
[36] Dienstmann R, Braña I, Rodon J, Tabernero J. Toxicity as a biomarker of efficacy of molecular targeted therapies: focus on EGFR and VEGF inhibiting anticancer drugs. Oncologist 2011;16:1729–40.
[37] Azizi M, Chedid A, Oudard S. Home blood-pressure monitoring in patients receiving sunitinib. N Engl J Med 2008;358:95–7.
[38] Bamias A, Manios E, Karadimou A, et al. The use of 24-h ambulatory blood pressure monitoring (ABPM) during the first cycle of sunitinib improves the diagnostic accuracy and management of hypertension in patients with advanced renal cancer. Eur J Cancer 2011;47:1660–8.
[39] Maitland ML, Bakris GL, Black HR, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. J Natl Cancer Inst 2010;102:596–604.
[40] Takahashi S, Kiyota N, Tahara M. Optimal use of lenvatinib in the treatment of advanced thyroid cancer. Cancers Head Neck 2017;2:7.
[41] James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507–20.
[42] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Cancer-related fatigue. Version 2; 2018 https://www.nccn.org/professionals/physician_gls/PDF/fatigue.pdf [Accessed October 3, 2018].
[43] Eisen T, Sternberg CN, Robert C, et al. Targeted therapies for renal cell carcinoma: review of adverse event management strategies. J Natl Cancer Inst 2012;104:93–113.
[44] Berdelou A, Borget I, Godbert Y, et al. Lenvatinib for the treatment of radioiodine-refractory thyroid cancer in real-life practice. Thyroid 2017 doi:10.1089/thy.2017.0205. [Epub ahead of print].
[45] Li J, Gu J. Risk of gastrointestinal events with newly approved (after 2011) vascular endothelial growth factor receptor tyrosine kinase inhibitors in cancer patients: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol 2017;73:1209–17.
[46] Aw DC, Tan EH, Chin TM, et al. Management of epidermal growth factor receptor tyrosine kinase inhibitor-related cutaneous and gastrointestinal toxicities. Asia Pac J Clin Oncol 2018;14:23–31.
[47] Cohen RB, Oudard S. Antiangiogenic therapy for advanced renal cell carcinoma: management of treatment-related toxicities. Invest New Drugs 2012;30:2066–79.
[48] Pilotte AP, Hohos MB, Polson KM, Huftalen TM, Treister N. Managing stomatitis in patients treated with mammalian target of rapamycin inhibitors. Clin J Oncol Nurs 2011;15:E83–9.
[49] Rugo HS, Seneviratne L, Beck JT, et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. Lancet Oncol 2017;18:654–62.
[50] Anderson J, Cuellar S. Updates in the use of the mTOR inhibitor everolimus in advanced breast cancer. J Cancer Clin Trials 2016;1:2.
[51] Lacouture ME, Ciccolini K, Kloos RT, Agulnik M. Overview and management of dermatologic events associated with targeted therapies for medullary thyroid cancer. Thyroid 2014;24:1329–40.
[52] 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. Oncologist 2008;13:1001–11.
[53] Chen HX, Cleck JN. Adverse effects of anticancer agents that target the VEGF pathway. Nat Rev Clin Oncol 2009;6:465–77.
[54] Armstrong TS, Wen PY, Gilbert MR, Schiff D. Management of treatment-associated toxicites of anti-angiogenic therapy in patients with brain tumors. Neuro Oncol 2012;14:1203–14.
[55] Kitamura M, Hayashi T, Suzuki C, et al. Successful recovery from a subclavicular ulcer caused by lenvatinib for thyroid cancer: a case report. World J Surg Oncol 2017;15:24.
[56] Verheul HM, Pinedo HM. Possible molecular mechanisms involved in the toxicity of angiogenesis inhibition. Nat Rev Cancer 2007;7:475–85.
[57] Silberstein JL, Millard F, Mehrazin R, et al. Feasibility and efficacy of neoadjuvant sunitinib before nephron-sparing surgery. BJU Int 2010;106:1270–6.
[58] Zhu C, Ma X, Hu Y, et al. Safety and efficacy profile of lenvatinib in cancer therapy: a systematic review and meta-analysis. Oncotarget 2016;7:44545–57.
[59] Andrae J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. Genes Dev 2008;22:1276–312.
[60] Ye JY, Chan GC, Qiao L, et al. Platelet-derived growth factor enhances platelet recovery in a murine model of radiation-induced thrombocytopenia and reduces apoptosis in megakaryocytes via its receptors and the PI3-k/Akt pathway. Haematologica 2010;95:1745–53.
[61] Kamba T, McDonald DM. Mechanisms of adverse effects of anti-VEGF therapy for cancer. Br J Cancer 2007;96:1788–95.
[62] Colombo JR, Wein RO. Cabozantinib for progressive metastatic medullary thyroid cancer: a review. Ther Clin Risk Manag 2014;10:395–404.
[63] Walraven M, Witteveen PO, Lolkema MP, et al. Antiangiogenic tyrosine kinase inhibition related gastrointestinal perforations: a case report and literature review. Angiogenesis 2011;14:135–41.
[64] Stone RL, Sood AK, Coleman RL. Collateral damage: toxic effects of targeted antiangiogenic therapies in ovarian cancer. Lancet Oncol 2010;11:465–75.
[65] Qi WX, Sun YJ, Tang LN, Shen Z, Yao Y. Risk of gastrointestinal perforation in cancer patients treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors: a systematic review and meta-analysis. Crit Rev Oncol Hematol 2014;89:394–403.
[66] Spigel DR, Hainsworth JD, Yardley DA, et al. Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. J Clin Oncol 2010;28:43–8.
[67] Blevins DP, Dadu R, Hu M, et al. Aerodigestive fistula formation as a rare side effect of antiangiogenic tyrosine kinase inhibitor therapy for thyroid cancer. Thyroid 2014;24:918–22.
[68] Stott VL, Hurrell MA, Anderson TJ. Reversible posterior leukoencephalopathy syndrome: a misnomer reviewed. Intern Med J 2005;35:83–90.
[69] Allen JA, Adlakha A, Bergethon PR. Reversible posterior leukoencephalopathy syndrome after bevacizumab/FOLFIRI regimen for metastatic colon cancer. Arch Neurol 2006;63:1475–8.
[70] Seet RC, Rabinstein AA. Clinical features and outcomes of posterior reversible encephalopathy syndrome following bevacizumab treatment. QJM 2012;105:69–75.
[71] Fugate JE, Claassen DO, Cloft HJ, et al. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. Mayo Clin Proc 2010;85:427–32.
[72] Tlemsani C, Mir O, Boudou-Rouquette P, et al. Posterior reversible encephalopathy syndrome induced by anti-VEGF agents. Target Oncol 2011;6:253–8.
[73] Hobson EV, Craven I, Blank SC. Posterior reversible encephalopathy syndrome: a truly treatable neurologic illness. Perit Dial Int 2012;32:590–4.
[74] Datar S, Singh T, Rabinstein AA, Fugate JE, Hocker S. Long-term risk of seizures and epilepsy in patients with posterior reversible encephalopathy syndrome. Epilepsia 2015;56:564–8.
[75] Ay H, Buonanno FS, Schaefer PW, et al. Posterior leukoencephalopathy without severe hypertension: utility of diffusion-weighted MRI. Neurology 1998;51:1369–76.
[76] Orphanos GS, Ioannidis GN, Ardavanis AG. Cardiotoxicity induced by tyrosine kinase inhibitors. Acta Oncol 2009;48:964–70.
[77] Tocchetti CG, Gallucci G, Coppola C, et al. The emerging issue of cardiac dysfunction induced by antineoplastic angiogenesis inhibitors. Eur J Heart Fail 2013;15:482–9.
[78] van Marcke C, Ledoux B, Petit B, Seront E. Rapid and fatal acute heart failure induced by pazopanib. BMJ Case Rep 2015;2015 pii: bcr2015211522. doi:10.1136/bcr-2015-211522.
[79] Lenihan DJ, Kowey PR. Overview and management of cardiac adverse events associated with tyrosine kinase inhibitors. Oncologist 2013;18:900–8.
[80] Mouhayar E, Durand JB, Cortes J. Cardiovascular toxicity of tyrosine kinase inhibitors. Expert Opin Drug Saf 2013;12:687–96.
[81] Resteghini C, Cavalieri S, Galbiati D, et al. Management of tyrosine kinase inhibitors (TKI) side effects in differentiated and medullary thyroid cancer patients. Best Pract Res Clin Endocrinol Metab 2017;31:349–61.
[82] Common Terminology Criteria for Adverse Events v3.0 (CTCAE). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf [Accessed October 3, 2018].