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GUIDELINES

Chinese consensus on management of tyrosine kinase inhibitor-associated side effects in gastrointestinal stromal tumors

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Abstract

Tyrosine kinase inhibitors (TKIs) have improved the overall survival of patients with gastrointestinal stromal tumors (GISTs), but their side effects can impact dose intensity and, consequently, the clinical benefit. To date, no guideline or consensus has been published on the TKI-associated adverse reactions. Therefore, the Chinese Society of Surgeons for Gastrointestinal Stromal Tumor of the Chinese Medical Doctor Association organized an expert panel discussion involving representatives from gastrointestinal surgery, medical oncology, cardiology, dermatology, nephrology, endocrinology, and ophthalmology to consider the systemic clinical symptoms, molecular and cellular mechanisms, and treatment recommendations of GISTs. Here, we present the resultant evidence- and experience-based consensus to guide the management of TKI-associated side events in clinical practice.

Key words: Side effects; Gastrointestinal stromal tumor; Tyrosine kinase inhibitors; Consensus guideline; China

Core tip: This is the first consensus focusing on tyrosine kinase inhibitor (TKI)-associated side effects in gastrointestinal stromal tumors (GISTs). The authors include not only oncologist, oncology surgeon, but also doctors from other relative specialties, such as cardiology, dermatology, nephrology, and endocrinology. The content consists of clinical symptoms, mechanisms, and management. Because except for GISTs, TKIs in this consensus are also used in other tumors, this consensus will be helpful to many oncologists in different specialties.

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INTRODUCTION

Tyrosine kinase inhibitors (TKIs), such as imatinib, sunitinib, and regorafenib, have significantly improved the overall survival of patients with gastrointestinal stromal tumors (GISTs). Their widespread use in clinical practice has provided evidence and experience from which we now may gain practical insight on further improving TKI efficacy and safety.

Maintaining continued drug administration at a sufficient dose is crucial for good efficacy. For GIST patients undergoing TKI therapy, the management of TKI-associated side effects is equally important. Fortunately, the symptoms of TKI-associated side effects are unique and can be exploited in the design of more effective and safe management protocols. The Chinese Society of Surgeons for Gastrointestinal Stromal Tumor of the Chinese Medical Doctor Association organized an expert panel discussion involving GIST-treating clinical doctors representing the various systemic components affected in our patient population including doctors from gastrointestinal surgery, medical oncology, cardiology, dermatology, nephrology, endocrinology, and ophthalmology. All treatment recommendations in this article are graded according to the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system, which is widely accepted to make evidence-based recommendations[1]. The final grade for the quality of evidence by the GRADE system is in Table 1.

This consensus guideline is intended to provide evidence- and experience-based expert recommendations on the management of TKI-associated side effects in GIST patients, in order to improve the efficacy and safety of TKI therapy. All the TKIs-associated side effects are summarized in Table 2.

TKI-ASSOCIATED SIDE EFFECTS

Edema and fluid retention

Edema is one of the most common adverse events (AEs) experienced by GIST patients undergoing TKI therapy. For imatinib, in particular, edema reportedly affects

Table 1 The grade for the quality of evidence by the Grades of Recommendation Assessment, Development and Evaluation system

Final grade rank	Definition of grade rank
High	We are very confident that the effect of the study reflects the actual effect
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible that it is substantially different
Low	The true effect may differ significantly from the estimate
Very low	The true effect is likely to be substantially different from the estimated effect

74.1% of patients[2]; in contrast, edema is rare and usually mild in patients receiving sunitinib[3]. The TKI-induced condition, in general, presents most frequently in the periorbital area or lower limbs.

Although there are reports of controlling the periorbital edema by limiting salt intake or administering topical phenylephrine or diuretics[4] (GRADE moderate), most cases of periorbital edema require no specific treatments. For patients with mild generalized or peripheral edema, it is important to perform regular weighing and monitoring to detect any event of unexpected weight gain or serious fluid retention[5] (GRADE moderate). Patients with more than a 3-kg weight gain in 1 wk should be counseled to reduce salt intake[6] (GRADE low). When supportive measures result in control of symptoms, reducing the dose of imatinib is not necessary (GRADE moderate).

Development of severe fluid retention, including pulmonary edema, pleural or pericardial effusion, and ascites or rapid weight gain, warrants prompt initiation or increased dose of a diuretic (GRADE moderate), although the risk of instigating electrolyte depletion necessitates a careful implementation of this approach. Regardless, imatinib should be discontinued in cases of severe fluid retention, and can be restarted once the edema is under control; diuretic therapy should be maintained throughout[7] (GRADE moderate).

Fluid retention may aggravate or cause heart failure. Patients with past histories of cardiac disease, cardiac failure, or renal impairment and associated risk factors should be monitored closely (GRADE moderate). Timely assessment will help to ensure initiation of proper treatments for patients as they present symptoms and signs of cardiac and/or renal failure (GRADE moderate).

Gastrointestinal AEs

Nausea and vomiting are the most common early AEs presenting in GIST patients treated with imatinib, sunitinib, or regorafenib[8]. The nausea and vomiting are often related, and most cases are reported as mild or moderate (grades 1-2). These AEs may be caused by the drugs' ability to induce release of neurotransmitters from the gastrointestinal tract and chromaffin cells, exciting the vagus nerves and sympathetic nerves and stimulating the vomiting center.

A prospective study of TKI-treated GIST patients reported in the literature identified vomiting as a remarkably common AE[9]. Imatinib-treated GIST patients have a reported incidence of nausea at 52.4% (1.4% representing grades 3-4) and of vomiting at 12.9% (0.7% representing grades 3-4)[2]. For regorafenib, the reported nausea incidence is 16% (1% representing grades 3-4)[10]; and, for sunitinib, the reported nausea incidence is 24% (1% representing grades 3-4) and vomiting incidence is 16% (1% representing grades 3-4)[11].

No special treatments are required when nausea and vomiting are mild or moderate. Dietary adjustment (GRADE moderate), however, can be used. In such cases, patients are advised to take a light diet consisting of acidic foods, fruit juices, *etc*., and to avoid eating sweet and greasy foods (GRADE moderate). If the AEs are grade 3 or 4, reducing dosage or suspending the drug administration is required. In such cases, more severe nausea and vomiting can be controlled effectively with antiemetic medications (GRADE high), such as metoclopramide, chlorpromazine, 5-hydroxytryptamine (5-HT_3) receptor blockers, and dexamethasone, among others. The TKI treatment can be reinstituted when the symptoms improve to grade 1.

Diarrhea is another common gastrointestinal side effect of the TKIs. While this AE is known to be dose-dependent, its underlying mechanisms remain to be fully elucidated[12]. The reported occurrence rate of diarrhea in patients treated with imatinib is 44.9% (2% representing grades 3-4)[2], with regorafenib is 40% (5% representing grade 3)[10], and with sunitinib is 29% (3% representing grades 3-4)[11]. For mild to moderate diarrhea (grades 1-2), the drug dose does not need to be reduced but dietary adjustment is required. Patients are recommended a light, easily digestible, vitamin-rich, low-fiber, high-protein diet, avoiding cold, spicy, and greasy foods (GRADE moderate).

In general, probiotics can be given occasionally to adjust the intestinal flora (GRADE moderate). For those patients whose diarrhea symptoms cannot be controlled or exacerbate, the TKI treatment should be suspended, and the patients should be given probiotics, berberine, montmorillonite, loperamide hydrochloride, and fluid and electrolyte support (GRADE high). The TKI treatment can be reinstituted when the symptoms improve to grade 1. At this point, the initial dosage can be reduced, if necessary.

Skin rash

Skin rash reportedly occurs in approximately 15% of GIST patients treated with sunitinib, presenting as mild symptoms; in contrast, up to 35% of GIST patients treated with imatinib experience skin rash (approximately 10% representing grades 3-4)[13,14]. For patiens taking imatinib, the likelihood of developing skin rash increases with increased 800 mg/d dose having a reported rash

Table 2 Summary of tyrosine kinase inhibitor-associated side effects

Side effects	Relative TKIs	Symptoms	Mechanisms	General management	TKIs - dose reduction or temporary discontinuation
Edema and fluid retention	Imatinib	Frequently in the periorbital area or lower limbs	Inhibiting PDGFR and decreasing the interstitial pressure	Limit salt intake or administer diuretics	Occasionally
Gastrointestinal adverse events	Imatinib, sunitinib, regorafenib	Nause, vomiting, and diarrhea	Inducing release of neurotransmitters, exciting the vagus nerves and sympathetic nerves	Antiemetic medications, Antidiarrhoeal medicine	Seldom
Skin rash	Imatinib, sunitinib	Erythematous and maculopapular lesions	Inhibiting of metabolic pathways mediated by tyrosine kinases	Topical lotions, antihistamines and steroids	Sometimes
Ophthalmological complications	Imatinib	Periorbital edema, epiphora, and hemorrhage in the conjunctiva	Inhibiting PDGFR and decreasing the interstitial pressure, conjunctival chemosis	Steroids and systemic diuretics	Not necessary
Hypertension	Sunitinib, regorafenib	Hypertension	Activating the endothelin axis and suppressing renin	ACEIs, ARAs	Sometimes
Hand-foot syndrome	Sunitinib, regorafenib	Bilateral palmar plantar erythema, skin peeling, and pain	Direct skin toxicity of TKIs, poor repair of small traumas due to VEGFR and PDGFR inhibition	Topical creams, keratolytic creams, emollients, analgesics	Often
Fatigue	Imatinib, sunitinib, regorafenib	Fatigue	5-HT$_3$ neurotransmitter disorder, proinflammatory cytokine accumulation, neuromuscular function degradation	Exercise intervention, nutritional support	Seldom
Proteinuria	Sunitinib, regorafenib	24 h urinary protein increase	VEGF inhibition	ACEIs, ARAs	Sometimes
Stomatitis	Sunitinib, regorafenib	Pain, edema, erythema, ulcers, burning sensation	Blockade of the VEGFR signaling pathway	Oral care, analgesics	Sometimes
Cardiotoxicity	Sunitinib, regorafenib	Q-T interval prolongation, decreased LVEF, etc	AMPK and PDGFR inhibition	ACEIs, diuretics	Often
Hypothyroidism	Sunitinib	Clinical or subclinical hypothyroidism	Destruction of the thyroid gland, inhibiting thyroid peroxidase activity, decreasing the density of thyroid capillaries	Sodium levothyroxine	Don't need
Hepatotoxicity and nephrotoxicity	Imatinib, sunitinib, regorafenib	Liver transaminase elevation, creatinine elevation	HBV reactivation, VEGF inhibition	Antiviral treatment, diammonium glycyrrhizinate	Sometimes
Hair disorder	Imatinib	Discoloration, trichomegaly, hypertrichosis, alopecia, etc.	Inhibition of kit pathway	No	Don't need
Interstitial lung disease	Imatinib	fever of unknown origin, cough, dyspnea, hypoxemia	Hypersensitivity reaction, inhibition of PDGFR	Sufficient corticosteroids, antibiotics	Discontiuation permanently in most cases
Hematological side effects	Imatinib, sunitinib, regorafenib	Anemia, neutropenia, thrombocytopenia	Inhibiting KIT-expressing hematologic stem cells	Ferrous sulfate, folate, G-CSF, TPO	Sometimes

TKI: Tyrosine kinase inhibitor; PDGFR: Platelet-derived growth factor receptor; ACEI: Angiotensin-converting enzyme inhibitor; ARA: Angiotensin Ⅱ receptor antagonist; VEGFR: Vascular endothelial growth factor receptor; 5-HT$_3$: 5-hydroxytryptamine; AMPK: 5' adenosine monophosphate-activated protein kinase; LVEF: Left ventricular ejection fraction; G-CSF: Granulocyte colony-stimulating factor; TPO: Thrombopoietin.

incidence of 46.6%[13].

While the underlying mechanism of these cutaneous reaction remains unclear, the high prevalence and dose dependence (of imatinib) suggest an association with a pharmacologic effect rather than a patient's hypersensitivity. Inhibition of various metabolic pathways mediated by tyrosine kinases, such as c-kit and platelet-derived growth factor receptor (PDGFR), could be involved in the pathophysiology of the adverse skin reactions[15]. Imatinib-induced skin rash commonly presents as erythematous and maculopapular lesions and may occur at any point throughout the treatment administration, but often occurs during the first week. The forearms or trunk are often affected, and may show pruritic and desquamated skin[4]. The skin rash may also be more common in female patients[15]. Severe cases may rarely lead to toxic epidermal necrolysis or Stevens-Johnson syndrome[4].

The most common sunitinib-related skin AE is dry skin (xerosis), reported in up to 16% of the treated GIST

patients. The less frequent events of sunitinib-induced rash can present as inflammatory follicular papules on the face and/or the trunk, or as a seborrheic dermatitis-like eruption similar to those associated with epidermal growth factor receptor (EGFR) inhibitors, but milder[16].

Rough or dry skin can be managed with observation (without treatment) or with treatment using topical lotions (GRADE moderate). In imatinib patients with mild to moderate rash, symptoms can be relieved with antihistamines and topical lotions. Steroids can be applied in patients with an inadequate response[4] (GRADE moderate). For recurrent grade 3 skin rash, dose interruption or reductions of imatinib should be required, along with oral steroid treatment, until the symptoms subside (GRADE high). The imatinib reinstitution should be initiated at low dosage. In those rare patients who experience severe skin reactions (*e.g.*, Stevens-Johnson syndrome), the imatinib administration should be interrupted (GRADE high). These patients can be treated with prednisone (starting at 1 mg/kg and tapering up to 20 mg/d, as needed), and the imatinib can be gradually reintroduced in the absence of alternative treatment options[4] (GRADE moderate).

It is worth noting that after reinstitution of an interrupted TKI drug, the patient may again develop a rash. A few patients will have drug hypersensitivity syndrome, exfoliative dermatitis, and bullous epidermolysis, possibly to a life-threatening extent, and need extra-medical attention.

Ophthalmological complications

Periorbital edema is the most common ocular side effect associated with imatinib, reported in up to 70% of treated GIST patients[2]. Dermal dendrocytes found in the periocular soft tissue express the tyrosine kinases c-kit and PDGFR. Through the inhibition of PDGFR, imatinib may decrease the interstitial pressure and increase transcapillary transport, causing edema[17,18].

Epiphora occurs in nearly 20% of imatinib-treated GIST patients, representing the second most common ocular side effect of this drug[19]. Postulated mechanisms for epiphora include conjunctival chemosis resulting in ocular surface irritation and the overproduction of tears, lacrimal pump dysfunction due to periorbital edema, blockage of the puncta by conjunctival chalasis, and secretion of the medication in the tear film[20]. Hemorrhage in the conjunctiva reportedly affects up to 11% of imatinib-treated GIST patients and occurs in the absence of marrow suppression or in those with systemic bleeding tendency[21,22]. Genetic polymorphisms of *EGFR*, *SLC22A1*, *SLC22A5*, and *ABCB1* may influence the imatinib-induced periorbital edema and conjunctival hemorrhage[22].

Sight-threatening complications affecting the optic nerve, macula, and retina are uncommon but do occur with imatinib. Imatinib has been shown to compromise the survival of retinal ganglion cells *in vitro*, *via* the inhibition of the PDGFR signaling pathway[23]. Other rare ophthalmological complications of imatinib include optic disc edema and optic nerve dysfunction, recurrent optic neuritis, cystoid macular edema, and retinal edema[24-26].

Most of the reported cases of periorbital edema and epiphora improve with topical steroids and systemic diuretics[27] (GRADE moderate). Surgical procedures, in the form of debulking excessive skin, fat, and edema, are required occasionally to resolve blurring eyesight resulting from periorbital swelling[28] (GRADE low). For conjunctival hemorrhage, most cases spontaneously recover or improve with topical steroids[29] (GRADE moderate). Disc edema and optic nerve dysfunction regress after cessation of the medication[23] (GRADE moderate). Macular edema and retinal edema subside with cessation of the medication, and optic neuritis improves with systemic steroids[24] (GRADE moderate).

Hypertension

Hypertension affects 11% or more of sunitinib-treated GIST patients (approximately 3% representing grades 3-4), whereas it occurs rarely during imatinib treatment[11,30,31]. Meanwhile, the incidence of sunitinib-induced hypertension in the Chinese GIST population is high, up to 28.8%; however, more severe cases, grades 3-4, remain low, at 3.4%[32]. Several mechanisms of sunitinib-induced hypertension have been identified, and these include activation of the endothelin axis, suppression of renin, decreased glomerular filtration rate, and increased sodium and water retention by the kidney[33-36].

Baseline blood pressure should be recorded before sunitinib therapy. The blood pressure monitoring is recommended to occur on a daily schedule during the sunitinib treatment, especially in the early period of treatment or for patients with a history of hypertension. In any case, hypertension management should involve antihypertensive agents, with a goal of achieving either normal blood pressure or grade 1 blood pressure (< 130/80 mmHg). Use of vasodilatory antihypertensive agents such as angiotensin-converting enzyme inhibitors (ACEIs, and including captopril, enalapril, benazepril, and gilazapril) as well as angiotensin Ⅱ receptor antagonists (ARAs, and including losartan potassium, valsartan, irbesartan, and telmisartan) are suggested for control of vascular endothelial growth factor receptor (VEGFR) inhibitor-associated hypertension of grade 2 or higher. Since some calcium channel blockers, such as diltiazem, verapamil, nitrendipine, and nifedipine, will increase sunitinib blood concentration (by inhibiting CYP450 3A4) or cause PR interval prolongation, they are not suggested for controlling high blood pressure caused by sunitinib or regorafenib[37,38] (GRADE high).

Generally, management of hypertension does not need dose reduction or interruption of sunitinib. In cases of severe hypertension (systolic blood pressure > 200 mmHg or diastolic blood pressure > 110 mmHg), sunitinib therapy should be temporarily ceased until the hypertension is under control (GRADE moderate).

Hand-foot syndrome

The AE of hand-foot syndrome (HFS) can occur during

sunitinib or regorafenib treatment, but has seldom been reported in GIST patients undergoing imatinib therapy. HFS rates for the first two drugs are 13.5%-25% for sunitinib and 56% for regorafenib at 4 wk into the TKI treatment administration[10,11,39-41], and it is one of the most frequent reasons for dose reduction of these TKIs. The main manifestations of TKI-induced HFS include bilateral palmar-plantar erythema accompanying dysesthesia, skin peeling, and pain (which can lead to dysfunction in daily activities and walking); moreover, a localized skin hyperkeratosis, especially at plantar site, may develop accompanied by callous[16].

The mechanism underlying TKI-induced HFS is not clear. HFS occurs in skin sites rich in eccrine glands, such as the palms and soles, due to a portion of the TKI being excreted in sweat. Two hypotheses proposed to explain the hand-foot skin reaction include direct skin toxicity of TKIs in general, and poor repair of repeated small traumas in hands and feet due to VEGFR- and PDGFR-inhibiting activity of sunitinib in particular[5].

Patient education is the first step of HFS management. Patients need to be able to recognize the clinical symptoms of HFS before receiving TKI treatment, to facilitate treatment at the earliest stage possible. Topical creams, keratolytic creams, or emollients can be useful to decrease HFS-related keratosis. Sufferers of TKI-induced HFS should be encouraged to use pressure-absorbing insoles and comfortable shoes or gloves when performing various activities. Analgesics may also be necessary to control HFS-related pain, until symptoms subside[42] (GRADE moderate). Administration of recombinant human fibroblast growth factor and/or recombinant human epidermal growth factor can help the recovery of skin damage (GRADE low).

In cases of grade 2 or 3 HFS, the TKI treatment should be temporarily interrupted. In severe cases of HFS, the TKI dosage must be reduced permanently. A study of HFS, sunitinib, and dosage showed an association between 50 mg/d (4 wk on, followed by 2 wk off) and severe AE cases, as compared to the schedule of 37.5 mg/d continuous therapy[10] (GRADE moderate).

Fatigue

Fatigue is a common AE of all three TKIs used in GIST patients, but it can be easily ignored since it is often accompanied by other symptoms. Yet, fatigue has serious impact on quality of life[43]. The incidence of fatigue is similar among the three TKIs, reportedly 34.7% with imatinib (all cases grade 1-2)[2], 39% with regorafenib (2% of cases representing grade 3)[10], and 34% with sunitinib (5% of cases representing grade 3)[11].

While the mechanisms of TKI-induced fatigue are not entirely clear, they are apparently complex. Among the hypothesized mechanisms are 5-hydroxy tryptamine neurotransmitter disorder, proinflammatory cytokine accumulation, and neuromuscular function degradation[44,45].

Cases of TKI-induced fatigue that are mild to moderate generally require no special treatment. However, if the fatigue reaches grade 3 or higher, active treatments should be initiated; these include reducing dosage or suspending administration of the drug, exercise intervention (such as yoga)[46] (GRADE low), massage, and acupuncture[47,48] (GRADE low). But caution should be taken for affected patients with bone metastases, thrombocytopenia, anemia, fever or active infections, *etc*. Psychological intervention and nutritional support can also be applied (GRADE low). Pharmacologic intervention with modafinil can be used in severe cases of fatigue (GRADE low), but this management strategy appears to be ineffective for mild to moderate cases[49].

Proteinuria

VEGF signaling pathway inhibitors are currently widely applied, as targeted therapy, for treating renal cancer, colorectal cancer, ovarian cancer and other advanced malignancies. The main role of these chemotherapeutic agents is to inhibit angiogenesis, and this chemotherapy approach includes use of monoclonal antibodies (such as bevacizumab) and small orally active TKIs (such as axitinib, sunitinib, and sorafenib). Proteinuria is one of the most frequently observed AEs of VEGF/VEGFR inhibitors.

The reported incidence rate of proteinuria has varied among different studies, according to differences in characteristics of the study population and tumor type under VEGF/VEGFR inhibitor treatment. In these cases, grade 1 proteinuria is defined as urinary protein of < 1.0 g in 24 h, grade 2 as urinary protein of 1.0-3.4 g in 24 h, and grade 3 as ⩾ 3.5 g in 24 h[50]. The highest risk of severe proteinuria was reported in patients with renal cell carcinoma (RCC), and the lowest risk is by patients with colorectal cancer[51].

The exact incidence of proteinuria in patients treated with small orally active VEGF TKIs is still undetermined. In trials with sorafenib, 21%-63% of the patients have presented asymptomatic mild proteinuria. Severe proteinuria cases have been reported in up to 6.5% of RCC patients[52]. VEGF signaling inhibition-induced proteinuria is typically asymptomatic and depends on dosage and time[53]. Incidence of proteinuria is also related to tumor type, kidney-associated chronic disease, drug-induced renal toxicity, and patient characteristics.

The mechanism underlying TKI-related proteinuria is not completely understood. There are few accepted theories. The first of such involves the role of VEGF in maintaining the glomerular filtration barrier, providing cytoprotection to the glomerular capillary endothelial cells. Inhibition of this protective effect through sunitinib-induced VEGF inhibition may, then, lead to proteinuria. A second theory involves the role of VEGF in down-regulating tight junction proteins on podocytes, thereby reducing kidney filtration function[54]. A third theory is based on VEGF signaling inhibition resulting in suppression of nephrin and leading to nephritic syndrome and glomerular thrombotic microangiopathy[5].

No guidelines exist for managing patients with suni-

tinib-specific proteinuria. Prior to beginning sunitinib therapy, all patients should undergo complete medical history-taking, physical examination, urinalysis, and urine sediment analysis. Currently, the majority of clinical researchers recommend ACEI or ARA therapy, which may reduce mild proteinuria (GRADE moderate). Antihypertensive drugs should be taken if the AE is accompanied by hypertension[55,56] (GRADE moderate).

The Kidney Disease Outcomes Quality Initiative recommends ACEIs or ARAs as first-line therapy for VEGF-associated proteinuria[57] (GRADE moderate). Discontinuation of sunitinib is recommended for patients with urinary protein levels > 3 g in a 24-h period (GRADE high). The sunitinib treatment can be restarted when the urinary protein level falls below that threshold[52] (GRADE high). The tumor and patient conditions should also be considered, as well as results of risk-benefit trend evaluation. Finally, it is crucial to obtain the informed consent of patients for this management.

Stomatitis

Targeted therapy-related stomatitis is characterized by pain, edema, erythema, ulcers, burning sensation when ingesting sour and spicy foods, and even anatomical dysfunction, such as difficulty in speech or dysphagia and loss of taste. Since the pathogenesis of stomatitis is associated with blockade of the VEGFR signaling pathway, this AE is rare during imatinib treatment but is common during sunitinib or regorafenib treatment. The reported incidence rates of stomatitis associated with sunitinib vary widely in the literature, ranging from 5% to 40.4%[58,59]. In the GRID phase Ⅲ trial (evaluating regorafenib in metastatic GISTs), however, stomatitis occurred in 38% of the treatment group, with only 2% developing grade 3 or above[10].

TKI-induced stomatitis is usually grade 1 or 2, and sometimes presents without definitive evidence or signs. The onset usually occurs within the first 1.9 mo of treatment[59].

Most of the cases do not need a dose modification or TKI withdrawal. Since stomatitis may lead to a decline in treatment compliance and the development of sepsis, it is necessary to pay attention to and help strengthen the patient's oral care by improving their oral hygiene, avoiding irritant food intake, and using mouth rinses (such as sodium bicarbonate); topical or systemic analgesics may be administered if necessary (*e.g.*, viscous lidocaine, benzocaine, or benzydamine)[5] (GRADE moderate).

If oral fungal infection is suspected, nystatin is recommended (rinse 4 times a day for 10 d). If grade 3 or 4 stomatitis occurs, the frequency of rinse application should be increased to 8-12 or more times per day (GRADE moderate). If there is no improvement after 1 wk, the TKI should be temporarily discontinued until the stomatitis attenuates to grade 1, then the drug could be resumed at the same dose (GRADE moderate).

Cardiotoxicity

TKI-related cardiac toxicity may present as asymptomatic Q-T interval prolongation, decreased left ventricular ejection fraction (LVEF), congestive heart failure, acute coronary syndrome, and myocardial infarction. Imatinib-related cardiac toxicity is rare. The incidence of heart failure in imatinib-treated GIST patients reported in the literature ranges from 0.5% to 1.7%, and cases are usually represented by the elderly (over 65 years old) with cardiac risk factors[60,61]. The mechanism underlying imatinib-induced cardiotoxicity may involve myocardial toxicity caused by c-Abl inhibition[62]. The rate of cardiac toxicity in sunitinib-treated GIST patients is higher than that of imatinib treatment, and the incidence of heart failure is reported to be 2.7%-15%[63-65], which needs to be paid more attention. The possible mechanisms of this sunitinib-induced cardiotoxicity include abnormality of mitochondrial energy metabolism induced by 5′ adenosine monophosphate-activated protein kinase (AMPK) inhibition in cardiac myocytes[66], and decreased myocardial adaption to afterload stress caused by inhibition of the PDGFR signaling pathway in cardiac myocytes. For regorafenib therapy, there is limited data on cardiac AEs. Although, in the GRID phase Ⅲ trial, there was one (0.8%) case of cardiac AE, it was grade 5 (cardiac arrest)[10].

Cardiac function evaluation should be considered when patients present signs of dyspnea and fatigue during the TKI therapy period. Patients with a history of coronary disease should undergo echocardiographic baseline LVEF measurement prior to sunitinib treatment and should be closely monitored for blood pressure and LVEF during the entire course of treatment. Hypertension should be treated with therapy including an ACE inhibitor (GRADE high). Patients with symptoms of chronic heart failure should be treated with ACE inhibitors and diuretics (GRADE high). In patients with a definitive diagnosis of heart failure, the sunitinib administration should be interrupted (GRADE high). Each patient needs to be assessed individually when the cardiac function has stabilized, with consideration given to available alternative treatments and the trade-off between the cardiac- and GIST-related risks. Reinstitution of sunitinib should start at a reduced dose (GRADE moderate).

For those patients with LVEF reduction to less than 50% during sunitinib treatment and without clinical symptoms of heart failure, the options include: (1) interruption of sunitinib treatment for several weeks; (2) sunitinib dose reduction; and (3) initiation of cardiac medication accompanied by close monitoring of cardiac function[5] (GRADE moderate).

Hypothyroidism

The incidence of hypothyroidism caused by sunitinib is higher. Clinical or subclinical hypothyroidism reportedly occurs in 53%-85% of GIST patients taking sunitinib[67-69].

The mechanism of sunitinib-induced hypothyroidism is not yet clear. Although studies have shown that during the sunitinib treatment, the thyroid uptake rate of I^{123} is reduced. Most of such AE cases return to normal uptake

rate after treatment completion, suggesting that the possible mechanism of this hypothyroidism involves an obstacle in the thyroid gland's ability to uptake iodine[70]. Some researchers have theorized that destruction of the thyroid gland by sunitinib is the main pathogenic mechanism of the related hypothyroidism[71]. In addition, sunitinib has been shown to inhibit thyroid peroxidase activity and to reduce thyroid hormone synthesis[72], which may support development of hyperthyroidism. It has also been suggested that the antiangiogenic effect of sunitinib may cause the observed decrease in the density of thyroid capillaries[73], leading to a toxic effect on the thyroid gland. *In vitro* experiments have also provided insights into the potential pathogenic mechanisms, and sunitinib was found to inhibit the transfection rearrangement/papillary adenocarcinoma kinase (RET/PTC) of the cell proliferation signaling pathway[74], which plays an important role in maintaining normal thyroid physiological function[75] and can induce hypothyroidism.

Thyroid dysfunction caused by sunitinib is more frequent in the early stage of treatment and most cases present transient thyrotoxicosis, manifesting as fatigue exacerbation and palpitation. However, as the treatment cycle is extended, the risk of hypothyroidism increases, and patients present with such symptoms as chills, drowsiness, and even myxedema coma. The mean duration of sunitinib-induced hypothyroidism is 50 wk. Sometimes, the clinical manifestations alone may not be sufficient to diagnose hypothyroidism in time and accurately. Thus, it is necessary to monitor thyroid function regularly in GIST patients undergoing sunitinib treatment. A number of studies[76-78] have found that the median progression-free survival in patients with sunitinib-induced hypothyroidism is longer than in those who retained normal thyroid function. Therefore, some scholars[79,80] have suggested thyroid function as an indicator of the efficacy of sunitinib in the treatment of GIST.

For GIST patients who are to receive sunitinib therapy, thyroid function should be assessed before the treatment initiation. For those with a past history of thyroid disease, the level of thyroid-stimulating hormone (TSH) should be monitored during the treatment course[42,81,82]; yet, the optimal TSH monitoring frequency and time have not been determined. Sunitinib-induced thyroid toxicity is usually not accompanied by clinical symptoms and is self-limiting (GRADE moderate). It is usually unnecessary to modify the dose or interrupt the administration of sunitinib (GRADE moderate). If severe symptoms of thyrotoxicosis develop or the patient presents with thyroid crisis, sunitinib should be discontinued and intervention measures should be taken (GRADE high). Patients with severe hypothyroidism can be treated with thyroid hormone replacement therapy, and the most commonly used alternative drug is sodium levothyroxine (GRADE high).

Hepatotoxicity and nephrotoxicity

Liver transaminase elevations are observed with TKI treatment[5,8]. Abnormal liver transaminase levels have been observed in about 5.4% of GIST patients receiving imatinib (2.7% representing grades 3 and 4)[2], and each case of imatinib-induced acute severe hepatotoxicity needs to be addressed seriously as it could cause hepatic failure or even death[83,84]. Liver function, as evidenced by measures of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin, should be assessed before treatment initiation and should be monitored periodically during the treatment period.

GIST patients with elevated AST/ALT levels should be monitored closely. Mild elevations can be monitored without administration of specific therapies or dose reduction. For patients with persistent grade 2 toxicity [AST/ALT at 2.5- to 5-fold upper limit of normal (ULN) value], a complete work-up to determine the cause of abnormal liver function is necessary (GRADE moderate). In patients with ongoing grade 2 toxicity, detailed evaluation is needed to determine dose reduction or interruption[4] (GRADE moderate). The current management of grade 3 or higher elevations in transaminases (AST/ALT at > 5-fold ULN) is to interrupt the TKI treatment (GRADE high). When the liver functions return to grade 1 or less (AST/ALT at < 2.5-fold ULN or bilirubin at < 1.5-fold ULN), the TKI administration can be reinstituted, but at a reduced dose (GRADE moderate). Specifically, the daily dose of imatinib should be reduced from 400 mg to 300 mg. The incidence of severe hepatotoxicity in sunitinib-treated patients is less than that in the imatinib-treated, and for sunitinib the dose can be decreased by 12.5 mg daily from the original dose when reinstituting the treatment[42] (GRADE low).

Hepatitis B is one of the most important public health issues in China, with almost 7.2% of China's population being chronically infected[85,86]. Considering the high prevalence of chronic hepatitis B in China, oncologists are likely to face patients who suffer from both GISTs and hepatitis B virus (HBV) infection. HBV reactivation is a well-recognized risk in patients with chronic HBV infection during chemotherapy and immunosuppressant therapy[87-90]. HBV reactivation can be severe and potentially fatal. There have been some reports of HBV reactivation in patients receiving imatinib[91-97]. HBV screening tests should be performed before receiving TKIs[98,99] (GRADE low). Prophylactic antiviral treatment should be offered to HBsAg-positive patients during treatment[98-100] (GRADE low). In addition, HBV virus load of anti-HBc-positive, HBsAg-negative patients could be monitored to assess the eventual reactivation of the occult disease[99] (GRADE low).

Nephrotoxicity has been observed rarely in GIST patients treated with TKIs. However, its monitoring should still be applied vigilantly during long-term treatment with TKIs, which may cause decline in kidney function. Cases of TKI-related acute kidney injury, chronic kidney disease, proteinuria, and nephrotic syndrome have been reported[101]. The monitoring of renal function should begin at treatment initiation and continue on a periodic schedule throughout the treatment course. When im-

paired kidney function is detected, it is necessary to consult a kidney specialist and evaluate the value of continuing TKI treatment (GRADE low).

Hair disorder

A pooled analysis of AEs experienced by GIST patients treated with TKIs revealed that the incidence of hair disorder is about 14%. The hair disorders reported have included discoloration, trichomegaly, hypertrichosis, alopecia, and madarosis. Compared with imatinib-treated patients, sunitinib-treated patients experience hair discoloration during treatment at a much more frequent rate (15.2%)[102]. Some researchers have reported that inhibition of kit pathway may reduce hair pigmentation. The functions of tyrosinase and tyrosinase-related protein 1, which are related to melanin synthesis, have been found to be impaired in TKI-treated patients as well[9] (GRADE high).

GIST patients receiving TKI treatment should be informed of the possibility of developing an uneven hair pigmentation AE. It is also necessary for patients to know that hair disorders associated with sunitinib are mostly mild and generally self-limiting, and that the AE will attenuate after cessation of treatment[9,10] (GRADE high).

Interstitial lung disease

Interstitial lung disease is a relatively rare AE during the TKI treatment of patients with GIST. However, once diagnosed, patients with TKI-induced interstitial lung disease need close medical attention and appropriate treatment. The incidence of interstitial lung disease among TKI-treated GIST patients is still unclear, due to a lack of research on this topic. According to a Japanese study of 5000 patients with chronic myeloid leukemia and 500 patients with GISTs receiving imatinib treatment, the overall incidence of interstitial lung disease was 0.5% and that in GIST patients was 0.8%[103]. The collective literature, albeit limited, suggests that interstitial lung disease may affect Asians more than other races and males more than females[104]. In addition, a history of interstitial lung disease is a risk factor for development of this AE during TKI therapy[105].

The mechanisms of TKI-induced interstitial lung disease remain debatable. The main hypotheses for such involve a hypersensitivity reaction, the pharmacological action of the TKI itself, and induced pulmonary fibrosis and inflammatory cell infiltration upon inhibition of PDGFR-A[106,107]. The symptoms are usually unspecific and present a few months into the treatment; these include fever of unknown origin, cough, dyspnea, hypoxemia, and hyper-eosinophilia. Chest X-ray, computed tomography (CT), and high-resolution CT may help to diagnose the interstitial lung disease. The typical CT characteristics are ground-glass opacity, irregular lining or reticular areas of formation with bronchiectasis and bronchiolectasis.

The success of treating TKI-induced interstitial lung disease depends on rapid and correct diagnoses. When a TKI-treated GIST patient presents with symptoms of interstitial lung disease (with possible infection or other causative factors excluded) and diagnosis of the disease is made, physicians should immediately discontinue the TKI treatment and treat patients with timely and sufficient corticosteroids, and antibiotics when necessary[108] (GRADE moderate). Although the severity of TKI-induced interstitial lung disease varies, it usually responds well to corticosteroid therapy[108] (GRADE moderate). After the symptoms have been relieved and imaging examination shows improvement of the disease condition, the physician should switch the patient to other drug regimens for treating the GIST. However, if no other therapies are available and the TKI is still effective, it should be continued under close monitoring. In such cases, the ratio of risk and benefit should be assessed carefully and the patients should be followed intensively[108] (GRADE moderate).

Hematological side effects

Anemia: Anemia is very common in GIST patients, both at the time of diagnosis and during the course of TKI treatment, especially for imatinib and when administered at high dosage (800 mg/d). A reported 16.7% of imatinib-treated patients present with grade 3-4 anemia[109], as compared to only 6.2% of sunitinib-treated patients[11]. GIST patients may have iron-deficiency anemia due to chronic gastrointestinal hemorrhage prior to surgery or small bowel resection. Meanwhile, gastrectomy and small bowel resection will cause vitamin B12 or folate deficiency, leading to megaloblastic anemia. Theoretically, TKIs may also inhibit KIT-expressing hematologic stem cells in the bone marrow.

Serum iron, ferritin, and transferrin levels, total iron binding capacity, folic acid, vitamin B12, and bilirubin should be detected in patients with GISTs. For patients with mild anemia (grade 1: blood hemoglobin $\geqslant$ 95 g/L), TKI interruption or other treatments are not necessary. For patients with grade 2 or higher anemia (blood hemoglobin level < 94 g/L), treatment regimens vary according to the anemia cause. For example, oral ferrous sulfate or intravenous administration of iron is suggested for patients with iron deficiency anemia, and vitamin B12 and folate are suggested for patients with megaloblastic anemia (GRADE high).

A high risk of thromboembolic events and high mortality rate from erythropoietin and darbepoetin alfa anemia therapies was found by meta-analyses[110,111]. As such, these drugs are only indicated when, after careful evaluation, the advantages outweigh the disadvantages. Red blood cell transfusion is only indicated for patients with acute hemorrhage or severe anemia, since its effects are transient and accompanied by transfusion-associated risks, such as transfusion reaction, virus transmission, and iron overload (GRADE high). The TKI dose does not need to be adjusted to address an anemia AE. Acute anemia should be evaluated for presence of hemorrhage in the gastrointestinal tract or peritoneal

cavity caused by the GIST itself, and emergency surgery should be considered. Once bleeding is under control, the initial dose of imatinib, sunitinib, or other TKIs can be reinstituted.

Neutropenia: Neutropenia is common in patients undergoing TKI therapy. The majority of these AEs are of grades 1-2. The rate of grades 3-4 neutropenia is around 7% with imatinib treatment and 10% with sunitinib treatment. Regardless of grade, the AE usually appears during the first 6 wk of treatment and remains stable afterwards[2,11,13].

For patients with grades 1-2 TKI-induced neutropenia, the TKI treatment can be continued at the initial dose and no specific management needs to be considered. If grades 3-4 neutropenia appear, administration of granulocyte colony-stimulating factor (G-CSF) is indicated and the TKI treatment should be suspended until the neutrophil count exceeds 1.5×10^6/L, at which time the initial daily dose should be reinstituted (GRADE high). Dose reduction of the TKI may be carried out in patients who experience repeated episodes of severe neutropenia (grades 3-4) or febrile neutropenia; for example, the dose of imatinib could be reduced from 400 mg daily to 300 mg daily or of sunitinib from 50 mg per day to 37.5 mg per day (GRADE high). Studies of G-CSF treatment in a mouse model of neutropenia indicated that the G-CSF may decrease the effect of anti-VEGF therapy[112]. These bench laboratory experimental results suggest that clinical administration of G-CSF and other granulocyte growth factors in combination with anti-VEGF therapies, such as sunitinib and regorafenib, should be carefully evaluated (GRADE moderate).

Thrombocytopenia: Thrombocytopenia is rarely observed in GIST patients receiving imatinib treatment (all grades: 6.3%; grade 3: 1.3%), but it is commonly seen in patients undergoing sunitinib therapy (all grades: 15.2%; grades 3-4: 5.7%)[2,11,13].

For patients with mild or moderate TKI-induced thrombocytopenia (grades 1-2), the TKI treatment can be continued at the initial dose and no specific treatment is needed. However, if the patient's blood platelet count falls below 50×10^9/L, recombinant human thrombopoietin (TPO) or interleukin-11 is indicated and the TKI treatment should be interrupted until the platelet count rises above 75×10^9/L, when it can be reinstituted at the initial daily dose (GRADE high). Dose reduction of TKIs may be carried out in patients with repeated episodes of severe thrombocytopenia (grades 3-4). The dose of imatinib at reinstitution can be reduced from 400 mg/d to 300 mg/d, and of sunitinib from 50 mg/d to 37.5 mg/d (GRADE high).

CONCLUSION

The AEs of TKI treatment are different in each GIST patient. Clinicians need to comprehensively assess the therapy's purpose and efficacy, the patient's tolerance, the types and severities of potential (and developed) AEs. Such assessments before TKI treatment initiation should be done with respect to the need for providing timely and effective treatment, so that the optimal efficacy of TKI treatment can be achieved and the patient's quality of life can be most protected and/or improved.

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