EDITORIAL

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Risks associated with sunitinib use and monitoring to improve patient outcomes

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Vascular endothelial growth factor (VEGF) plays an essential role in tumor growth, invasion, and angiogenesis and has emerged as an important target in cancer drug development [1]. The use of VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs) is a major step forward in the treatment of several malignancies and has improved patient outcomes significantly [2]. The U.S. Food and Drug Administration (FDA) has approved four VEGF TKIs for use in cancer therapy: sunitinib (Sutent, Pfizer, New York, NY, USA), sorafenib (Nexavar, Bayer Pharmaceuticals, West Haven, CT, USA; and Onyx Pharmaceuticals, Richmond, CA, USA), pazopanib (Votrient, GlaxoSmithKline, Middlesex, UK), and vandetanib (Caprelsa, AstraZeneca, London, UK). However, VEGFR TKIs are associated with a significant increase in the risk of fatal adverse events (FAEs) in patients with advanced solid tumors. An analysis of 5,164 patients across 13 randomized controlled trials (RCTs) revealed that the relative risk was 1.64 (95% confidence interval, 1.16 to 2.32; $p = 0.01$; incidence, 2.26% vs. 1.26%) for the association of a VEGFR TKI with FAEs using a random effects model [3].

Sunitinib is approved for the treatment of renal cell carcinoma (RCC) and gastrointestinal stromal tumors (GIST) [4,5] and should be administered as a 50-mg oral dose taken once daily on a schedule of 4 weeks on treatment followed by 2 weeks off. RCC patients receiving sunitinib experienced a significantly longer progression-free survival than those receiving interferon (IFN)-α (11 months vs. 5 months; $p < 0.001$). However, there are also adverse events. Frequent adverse events in patients treated with sunitinib included constitutional symptoms such as fatigue and gastrointestinal symptoms such as diarrhea, nausea, mucositis, stomatitis, and vomiting. Patients on sunitinib had significantly higher rates of diarrhea, vomiting, hypertension, and hand-foot syndrome (HFS), as well as leukopenia, neutropenia and thrombocytopenia than patients treated with IFN-α alone. In addition, sunitinib was associated with a left ventricular ejection fraction (LVEF) decline and thyroid dysfunction, mainly hypothyroidism. Consequently, routine monitoring is warranted during treatment [6,7].

In this journal, Baek et al. [8] found that the incidence of renal adverse effects (RAEs) associated with sunitinib was lower than in previous reports. The severity of RAEs was mild to moderate and they were partially reversible after stopping sunitinib. Therefore, they suggest that blood pressure, uri-

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nalysis, and renal function be monitored closely in patients receiving sunitinib [8]. The reported incidence of mild and asymptomatic proteinuria ranges from 21% to 63%, while heavy proteinuria is reported in up to 6.5% of RCC patients. Although discontinuing the anti-VEGF agent will significantly reduce the proteinuria, persistence is common [9]. The podocyte slit diaphragm has an important, direct role in glomerular filtration. Some of its protein components are involved in the mechanism of proteinuria, including nephrin, NEPH, FAT, podocin, and CD2-associated protein. Inactivation of these protein genes in mice causes massive proteinuria and, sometimes, the absence of a slit diaphragm and death. Studies of genetically modified mice suggest that podocyte-derived VEGF plays a major role in the development of the endothelium and the maintenance of its fenestrations [9,10]. No sunitinib-specific guidelines exist for managing patients zof sunitinib is recommended in patients with urinary protein levels > 3 g in a 24-hour period. Sunitinib treatment can be restarted when the urinary protein level falls below this level [2].

Cardiovascular events reported in patients on sunitinib therapy include heart failure, myocardial disorders, and cardiomyopathy [2]. Platelet-derived growth factor receptors (PDGFRs) are expressed on cardiomyocytes, and their overexpression can signal survival. Conversely, the inhibition of PDGFR can cause apoptosis [11]. A full cardiovascular assessment should be performed before initiating treatment and should include a baseline electrocardiogram (ECG) and LVEF evaluation. Clinicians should weigh the benefits of sunitinib against the potential risks before prescribing treatment to patients with cardiac risk factors or a history of coronary artery disease [2]. On sunitinib treatment, the patients should be monitored periodically with an ECG and LVEF evaluation at baseline and every 3 months, independently of any history of cardiovascular disease. Moreover, sunitinib is contraindicated in patients with a forced expiratory volume in one second < 50% at baseline and it should be discontinued when the LVEF decreases > 20% below baseline during treatment [6].

Myelosuppression can occur with sunitinib, including neutropenia and thrombocytopenia. While the exact mechanism of sunitinib-related myelosuppression is unknown, evidence suggests that Flt-3, c-Kit, and VEGF play a role. Flt-3 and c-Kit receptors are expressed on hematopoietic progenitor cells and are essential to the optimal production of mature hematopoietic cells. There are subtle differences in the potencies or TKIs against c-Kit and Flt-3, with sunitinib having the highest affinity for both of these. Sorafenib had modest activity against both c-Kit and Flt-3 kinases [12]. At the start of treatment, patients should be advised of the importance of good hygiene and diet, as well as educated on measures to minimize the risk of infection, including washing hands often, always washing hands after using the bathroom, and avoiding crowds and people who are sick. A complete blood count (CBC) should be determined before treatment and at week 4. For grade 3 to 4 myelosuppression, sunitinib treatment should be interrupted. The sunitinib can be restarted when the CBC returns to normal. For a grade 4 adverse event, the dosage should be reduced by one level [2].

The molecular mechanisms of sunitinib-induced hypothyroidism are currently unknown. Sunitinib might have a direct effect on the thyroid, possibly through the inhibition of VEGFR or PDGFR. VEGFR inhibition can induce capillary regression in the thyroid and can also increase thyroid stimulating hormone (TSH) levels [13]. Sunitinib can also inhibit thyroid peroxidase leading to reduced thyroid hormone synthesis, as suggested by *in vitro* studies [14]. Indirectly, sunitinib can affect the thyroid by interfering with the metabolism of T4/T3 hormones, or with thyroid hormone action at the pituitary level. In patients treated with the TKI sorafenib, thyroid dysfunction seems to be an infrequent side effect [15]. It is recommended that all patients treated with sunitinib have thyroid function tests performed on days 1 and 28 of the first four cycles. This intensive initial screening can detect patients at risk of developing sunitinib-induced thyroid dysfunction early. Hormone replacement should be started in patients with a persistent TSH > 10 mIU/L and a low or normal T4, but with typical symptoms of hypothyroidism. As the TSH level declines, and it can normalize by the end of the 2-week of rest in a sunitinib cycle, the decision to start hormone replacement should be based on the TSH level on day 1 of the new sunitinib cycle, rather than on day 28 of the current cycle, to avoid overtreatment [13].

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The mechanisms of sunitinib-associated hepatotoxic and gastrointestinal toxicities are unknown. The incidence of sunitinib-associated hepatotoxicity is low, with liver failure observed in 0.3% of clinical trial patients. Signs of liver failure include jaundice, elevated transaminases or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and renal failure [2,16]. The global incidence of diarrhea is 44% to 61% for all grades and 5% to 9% for grades 3 to 4. Rates appear to be similar among Asian groups [2].

HFS, also known as palmar-plantar erythrodysesthesia, is a painful erythematous condition occurring most commonly on the pressure and flexure points of the hands and feet. Existing hyperkeratotic areas tend to predispose patients to the development of HFS, which appears to be dose-dependent and tends to occur in the first 2 to 4 weeks of treatment [2,16]. It is hypothesized that epidermal keratinocytes synthesize PDGF, activating ligands for PDGFR in the dermal capillaries, fibroblasts, and eccrine glands [16,17]. The global incidence of HFS in sunitinib-treated patients is 24% to 29% [18,19]. Reports from Asian centers suggest that the incidence is higher for Asian patients [2]. The severity of HFS experienced by sunitinib-treated patients tends to decease gradually as the treatment duration increases. Therefore, aggressive management is recommended during the first few treatment cycles in order to minimize the effects of this adverse effect and maximize the dose and duration of sunitinib in order to produce the best possible therapeutic outcome [2].

In conclusion, the use of small-molecule VEGFR TKIs is associated with a significant increase in the risk of developing adverse events. It is important to remember the drug benefit to the patient with RCC or GIST, and TKIs should continue to be offered to these patients. However, we must be aware of the risks associated with their use and provide rigorous monitoring to continue to improve patient outcomes.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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