

REVIEW ARTICLE

Targeted therapies in the treatment of GIST: Adverse events and maximising the benefits of sunitinib through proactive therapy management

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Abstract

Background and objectives. The introduction of targeted therapies has led to improved clinical outcomes in patients with unresectable gastrointestinal stromal tumours (GIST). The receptor tyrosine kinase (RTK) inhibitor imatinib mesylate has been approved as the first-line choice of therapy for this group of patients, while the RTK inhibitor, sunitinib malate, has been approved for the treatment of GIST after disease progression or intolerance to imatinib. Here we discuss and compare the tolerability profiles of imatinib and sunitinib based on published clinical trial data. We also review available data on the potential mechanisms by which these agents may cause adverse events (AEs) and we propose some general strategies to help clinicians to optimise treatment benefit with these agents. **Findings.** While the toxicity profiles of imatinib and sunitinib are well known, the mechanisms of toxicity of these agents have yet to be elucidated fully. Clinical observations along with retrospective and prospective analyses suggest that some RTK inhibitor-related AEs have a higher incidence than previously reported from clinical trials. In addition, with greater use, new and unexpected AEs are emerging. Clinicians need to be familiar with the toxicity profiles of RTK inhibitors as well as individual patient risk factors in order to optimise treatment benefit. **Conclusions.** Imatinib and sunitinib are generally well tolerated with known and manageable AE profiles. Proactive therapy management strategies can enable treatment optimisation and allow patients to continue treatment with minimal interruption.

Unresectable gastrointestinal stromal tumour (GIST) is associated with poor response rates to conventional chemotherapy or radiotherapy [1]. In recent years, receptor tyrosine kinase (RTK) inhibitors have been shown to improve clinical outcomes in most patients and are now considered standard treatment for unresectable and/or metastatic GIST. Imatinib mesylate (Glivec®), an RTK inhibitor of stem-cell factor receptor (KIT) and platelet-derived growth factor receptor- α (PDGFR- α) [2], is the first-line choice for the treatment of KIT-positive unresectable and/or metastatic GIST [3,4].

Sunitinib malate (SUTENT®), an oral multitargeted RTK inhibitor of KIT, PDGFR- α and - β , vascular endothelial growth factor receptors (VEGFR-1, -2, and -3), FMS-like tyrosine kinase 3 (FLT3), colony-stimulating factor 1 receptor (CSF-1R) and glial cell line-derived neurotrophic factor receptor

(REarranged during Transfection; RET) [5–10], has demonstrated efficacy in treating patients with GIST who have experienced disease progression on or intolerance to imatinib [11]. Sunitinib has been approved multinationally for the treatment of advanced and/or metastatic renal cell carcinoma (RCC) and for unresectable and/or metastatic GIST after disease progression on or intolerance to imatinib therapy [12].

In phase III clinical trials, imatinib 800 mg/day has also shown benefit in patients resistant to imatinib 400 mg/day, but with increased toxicity as compared with the standard dose of imatinib [13,14]. To date, no published trials have compared the efficacy and toxicity of sunitinib and high-dose imatinib in patients with GIST who showed disease progression while receiving imatinib. However, this is the focus of an ongoing

phase III study, which is currently enrolling patients [15]. Other studies into the efficacy and safety of sunitinib in patients with imatinib-resistant/-intolerant GIST are both planned and ongoing [16–18].

As RTK inhibitor therapy for GIST is commonly administered over a long period, clinicians need to be familiar with the toxicity profiles of targeted agents as well as individual patient risk factors in order to proactively manage adverse events (AEs) and optimise long-term treatment benefit. Prompt prescription of symptom-control measures can improve patient quality of life and may positively influence adherence to treatment. Patient awareness and education are key to managing expectations and maximising the benefits of therapy.

This review examines the use of RTK inhibitors in patients with advanced GIST, with a particular focus on the tolerability and safety profiles of sunitinib and imatinib. In the absence of direct comparative trials, the comparisons between imatinib and sunitinib are based on historical comparisons of published study results. We also consider the likely mechanisms of toxicity with these agents. Finally, we focus our discussions on the management of sunitinib treatment in order to optimise treatment benefit.

Sunitinib and imatinib tolerability in GIST

To date, no direct comparisons between sunitinib and imatinib have been made in terms of safety and tolerability. Although the overall toxicity profiles of these two agents appear to be generally comparable, important differences have been noted, for example, in terms of the incidence and severity of hypothyroidism, hair and skin pigmentation, skin reactions, oedema, hypertension and hand-foot syndrome. Furthermore, administration of imatinib at the higher dose of 800 mg/day has been associated with a significantly higher incidence of toxicity compared with the 400 mg/day dose [13,14].

Sunitinib

The tolerability of sunitinib has been reported in a number of studies, including preclinical [12,19], phase I/II [20] and phase III clinical [11] trials, a treatment-use study [17] and a CDD study [16]. In general, AEs have been manageable and mild-to-moderate in nature.

Preclinical studies. In preclinical toxicity studies, adrenal toxicity (cortical congestion, haemorrhage

or necrosis), bone marrow depletion and effects on the pancreas were seen in rats and monkeys [12,19]. In addition, vomiting and diarrhoea occurred in monkeys, and slight increases in arterial blood pressure and QT interval were observed at higher doses [12]. Left ventricular ejection fraction (LVEF) reduction and haemorrhage in the gastrointestinal (GI) tract and oral mucosa were also noted [12].

Phase I/II and phase III studies. In a phase I/II trial with sunitinib in patients with imatinib-resistant/-intolerant GIST (N=97), the most commonly reported treatment-related AEs were grade 1–2 fatigue, diarrhoea, skin discoloration, nausea and hand-foot syndrome [20]. Treatment-related grade 3–4 AEs included hypertension (17%), asymptomatic lipase increase (13%) and fatigue (10%). Eight patients (8%) discontinued treatment due to AEs [21].

In a phase III randomised controlled trial of sunitinib in patients (N=312) with imatinib-resistant/-intolerant advanced GIST, treatment-related AEs were reported in 83% (n=168) of patients in the sunitinib group and 59% (n=60) in the placebo group [11]. An updated analysis of this study (N=361; n=243, sunitinib; n=118, placebo) reported the incidence of treatment-related AEs for the blinded, unblinded and overall populations [22]. The profile of AE observed was similar to that of the phase I/II study. Moreover, similar incidences of AEs were observed in the blinded and unblinded populations (Table I). A slightly higher incidence of non-haematological AEs was noted with longer duration of sunitinib therapy. Treatment-related hypothyroidism (all grades) was reported in 13% of patients. Most haematological laboratory abnormalities were grade 1–2 and were similar in frequency to those occurring with shorter-term sunitinib therapy.

In the blinded phase of the phase III trial, discontinuations due to AEs occurred in 9% (n=23) of patients in the sunitinib group and 3% (n=4) of patients in the placebo group [22]. In addition, dose reductions were required in 12% (n=27) of patients receiving sunitinib (compared with none in the placebo group) and treatment interruptions were required in 28% (n=65) of patients receiving sunitinib and 12% (n=14) of those receiving placebo. AEs were the reason for treatment interruption in 23% (n=54) and 9% (n=10) of patients in the sunitinib and placebo groups, respectively [22].

Table I. Most common (>15%) treatment-related adverse events associated with sunitinib versus placebo therapy in patients with advanced imatinib-refractory gastrointestinal stromal tumours [22].

Adverse event	Blinded phase			Open-label phase			Blinded + open-label phases		
	Sunitinib (n=235)			Placebo (n=115)			All patients [†] (n=247)		
	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 3/4 n (%)
Fatigue	71 (30)	19 (8)	24 (21)	2 (2)	97 (39)	25 (10)	88 (37)	25 (10)	25 (10)
Diarrhoea	73 (31)	8 (3)	9 (8)	0 (0)	77 (31)	11 (4)	92 (38)	12 (5)	12 (5)
Nausea	63 (27)	3 (1)	14 (12)	2 (2)	71 (29)	9 (4)	82 (34)	6 (2)	6 (2)
Anorexia	47 (20)	0 (0)	5 (4)	1 (1)	55 (22)	6 (2)	64 (27)	2 (1)	2 (1)
Dysgeusia	50 (21)	0 (0)	3 (3)	0 (0)	54 (22)	1 (0.4)	60 (25)	1 (0.4)	1 (0.4)
Vomiting	39 (17)	1 (0.4)	7 (6)	1 (1)	43 (17)	5 (2)	51 (21)	3 (1)	3 (1)
Yellow skin	42 (18)	0 (0)	5 (4)	0 (0)	51 (21)	0 (0)	49 (20)	0 (0)	0 (0)
Mucosal inflammation	34 (14)	2 (1)	0 (0)	0 (0)	40 (16)	5 (2)	44 (18)	4 (2)	4 (2)
Hypertension	21 (9)	11 (5)	5 (4)	1 (1)	36 (15)	19 (8)	29 (12)	18 (7)	18 (7)
Rash	35 (15)	2 (1)	6 (5)	0 (0)	36 (15)	1 (0.4)	43 (18)	3 (1)	3 (1)
Stomatitis	36 (15)	1 (0.4)	1 (1)	0 (0)	35 (14)	4 (2)	42 (17)	3 (1)	3 (1)
Dyspepsia	34 (14)	1 (0.4)	1 (1)	0 (0)	42 (17)	2 (1)	43 (18)	1 (0.1)	1 (0.1)
Headache	24 (10)	1 (0.4)	7 (6)	0 (0)	43 (17)	3 (1)	41 (17)	3 (1)	3 (1)
Hand-foot syndrome	19 (8)	9 (4)	1 (1)	0 (0)	44 (18)	13 (5)	30 (12)	14 (6)	14 (6)
Asthenia	28 (12)	6 (3)	2 (2)	2 (2)	28 (11)	12 (5)	30 (12)	13 (5)	13 (5)
Hair colour changes	20 (9)	0 (0)	2 (2)	0 (0)	49 (20)	0 (0)	37 (15)	0 (0)	0 (0)
Laboratory abnormalities									
Haemoglobin	125 (53)	9 (4)	60 (52)	2 (2)	71 (29)	4 (2)	132 (55)	11 (5)	11 (5)
Neutrophils	106 (45)	24 (10)	4 (3)	0 (0)	58 (23)	16 (6)	113 (47)	28 (12)	28 (12)
Platelets	86 (37)	9 (4)	3 (3)	0 (0)	46 (19)	3 (1)	90 (37)	10 (4)	10 (4)

*Based on the sunitinib arm over the entire study;

[†]per-protocol population;[‡]treatment=sunitinib;[§]five grade 5 events deemed to be treatment-related occurred in this group (hepatic failure, left ventricular failure, cardiac arrest, cerebral ischaemia, and multi-organ failure).

Treatment-use study. An ongoing treatment-use study (N=1 126 patients) [17] has allowed access to sunitinib to patient populations with advanced GIST who would otherwise be ineligible to participate in clinical trials; this study is clarifying sunitinib tolerability in a wider patient population than has previously been studied.

At last analysis, fatigue (42%, n=465), diarrhoea (39%, n=439) and nausea (28%, n=315) were the most common treatment-related grade 1–2 AEs associated with sunitinib therapy in this study [17]. The most common grade 3–4 AEs were fatigue (8%, n=91), hand–foot syndrome (8%, n=88), hypertension (5%, n=60) and diarrhoea (5%, n=55). Treatment-related hypothyroidism (all grades) occurred in 10% of patients. The incidences of grade 3–4 cardiac-related events such as heart failure, congestive heart failure, myocardial infarction, pulmonary oedema, and reduced ejection fraction were low (all $\leq 0.6\%$). Grade 3–4 treatment-related haematological abnormalities included neutropenia (7%, n=82) thrombocytopenia (5%, n=57), and anaemia (5%, n=51).

In this study, 19% (n=214) of patients discontinued treatment due to AEs, and dose reductions (for any reason) occurred in 42% (n=465) of patients.

Continuous dosing study. In a study of CDD of sunitinib 37.5 mg in patients with advanced GIST (N=60) [16], the AE profile was consistent with that seen in the earlier phase III trial [22]. The most common treatment-related AEs of any cause included diarrhoea, fatigue, asthenia and nausea (42%, 37%, 33% and 27%; respectively). No grade 4 events were reported. Grade 3–4 haematological laboratory abnormalities included neutropenia (15%, n=9), anaemia (12%, n=7) and thrombocytopenia (7%, n=4). Morning and evening dosing were associated with comparable levels of toxicities.

Treatment discontinuations due to AEs were required in 3% (n=2) of patients and dose reductions to 25 mg in 23% (n=14) of patients in the CDD study. Of note, the percentage of treatment discontinuations and/or dose reductions with CDD were less than reported with the intermittent Schedule 4/2 (6-weeks cycles of 4 weeks on treatment, followed by 2 weeks off treatment) in the phase III trial and treatment-use study [17,22].

Cardiotoxicity and sunitinib treatment. In contrast to the above-mentioned initial clinical trials, recent retrospective and prospective analyses have revealed previously unanticipated cardiac-related AEs of sunitinib.

A recent retrospective analysis of all cardiovascular events occurring in the 75 patients enrolled in the phase I/II GIST trial at Harvard Medical School [23] found that 11% (n=8) of patients experienced a cardiovascular event, 8% (n=6) had congestive heart failure (CHF) and 47% (n=35) developed hypertension ($>150/100$ mmHg). Of the 36 patient treated with the approved dose of sunitinib, 19% (n=7) had a reduction in LVEF of at least 15% and 6% (n=2) had a reduction of at least 20%.

These results indicate a higher incidence of cardiotoxicity than was reported in patients randomised to sunitinib in the phase III GIST study (treatment-related hypertension (all grades) 19%; all grade cardiac AEs 6%) [22]. Explanations for these differences may include differences in study populations, prior treatment history and methods of data collection used.

The summary of product characteristics (SmPC) for sunitinib [24] notes that approximately 2% of sunitinib-treated GIST patients exhibit decreases in LVEF of up to 20% or more below the lower limit of normal. Furthermore, cardiac treatment-related AEs ('cardiac failure', 'cardiac failure congestive' or 'left ventricular failure') were reported in 0.7% of patients with GIST receiving sunitinib and in 1% of patients receiving placebo treatment [24].

The mechanism by which RTK inhibitors might induce cardiac dysfunction is poorly understood. A recent report from an observational, single-centre study of patients with metastatic RCC receiving either sunitinib or sorafenib, suggests that cardiotoxicity caused by RTK therapy is largely underestimated but is manageable with careful cardiovascular monitoring and timely treatment [25]. A prospective study of cancer patients to try to detect heart damage during treatment with sunitinib or sorafenib is ongoing [26]; the results may shed some light on this phenomenon.

The SmPC for sunitinib recommends close cardiac monitoring in patients treated with sunitinib, especially in those with cardiac risk factors and/or history of coronary artery disease [24].

Thyroid dysfunction and sunitinib treatment

Until recently, thyroid dysfunction was considered to be an uncommon drug-induced AE of anticancer therapy. However, updated analysis of long-term data from the phase III trial suggests that the incidence is higher than previously reported [22]. In addition, an independent study by Desai et al. reported abnormal serum thyroid stimulating hormone (TSH) concentrations following sunitinib treatment in up to 62% of GIST patients; 36% developed primary hypothyroidism [27]. Other groups

have reported similar rates of abnormal thyroid function tests (TFTs) in patients with advanced GIST receiving treatment with sunitinib [28–30].

However, most of the studies were retrospective, hypothyroidism was not clearly defined in all studies and the TSH reference values differed. In addition, the timing of TSH measurements in relation to the sunitinib treatment cycle varied, and reliable data on the prevalence of hypothyroidism in the general cancer patient population are not available for comparison [29].

Though all the above factors may affect the interpretation of reported rates of thyroid dysfunction in sunitinib-treated patients with GIST, a prospective study suggests that thyroid function should be routinely monitored in patients receiving sunitinib treatment; 47% of patients with GIST in the study developed thyroid dysfunction, of which 12% required therapeutic intervention [29].

The SmPC for sunitinib recommends baseline monitoring of thyroid function and throughout treatment for signs of signs and/or symptoms suggestive of thyroid dysfunction [24]. The SmPC further recommends that patients presenting with thyroid dysfunction before or during treatment should be treated as per standard medical practice.

Other and rare AEs with sunitinib. With wider use of sunitinib, other rare, unexpected and in some cases, potentially serious, AEs that clinicians need to be aware of are emerging. We note here some of these AEs reported in patients with GIST.

Cutaneous AEs, including hand–foot syndrome, are commonly reported in patients treated with sunitinib [31,32]. The clinicopathological characteristics of hand–foot syndrome have been demonstrated to correlate with time of treatment exposure [33]. While hand–foot syndrome is not a life-threatening condition, it can severely impact quality of life and lead to dose modification or treatment interruption, which may affect clinical outcomes [33,34].

Table IIa. Comparison of toxicities associated with imatinib therapy at doses of 400 mg/day and 800 mg/day in patients with advanced gastrointestinal stromal tumours in the a) North American phase III study.

Adverse event, n (%)	Imatinib 400 mg/day (n=344)	Imatinib 800 mg/day (n=347)
Blood/bone marrow	68 (20)	92 (27)
Cardiovascular	23 (7)	48 (14)
Constitutional symptoms	14 (4)	30 (9)
Dermatology/skin	14 (4)	26 (7)
Gastrointestinal	31 (9)	54 (16)
Haemorrhagic	18 (5)	38 (11)
Hepatic	12 (3)	13 (4)
Infection/febrile	15 (4)	23 (7)
Pain	37 (11)	42 (12)

There have also been several reports of reversible posterior leukoencephalopathy syndrome (RPLS) in patients treated with sunitinib including one GIST patient [35]. There has also been one report of tumour lysis syndrome in a patient with metastatic GIST who was treated with sunitinib [36].

Imatinib

The toxicity profile of imatinib has been demonstrated in a phase I/II study [37,38] and two phase III trials [13,14] in patients with metastatic GIST; these trials also compared the imatinib 400 mg/day dose with higher 600 and 800 mg/day dosing strategies.

Phase I/II study. In a phase II trial of imatinib 400 mg/day versus 600 mg/day in patients with metastatic GIST (N=147) [38], the most commonly reported treatment-related AEs were oedema (74%, n=109), nausea (52%, n=77), diarrhoea (45%), myalgia/musculoskeletal pain (40%, n=58) and fatigue (35%, n=51). The most common grade 3–4 non-haematological AEs were haemorrhage (5%, n=7), dermatitis/rash (3%, n=4) and abnormal liver function results (3%, n=4). Grade 3–4 haematological abnormalities reported most commonly were neutropenia (5%, n=7), anaemia (2%, n=3) and leucopenia (1%, n=2).

Phase III studies. In the two phase III trials (North American, N=746 [13]; Euro-Australasian, N=946 [14]) of imatinib 400 mg/day versus 800 mg/day dosing in patients with metastatic GIST, imatinib doses of more than 400 mg/day were associated with dose-related increases in toxicity. In the North American trial [13], reported grade 3–5 non-haematological AEs included gastrointestinal (lower versus higher dose, 9% versus 16%), cardiovascular (7% versus 14%) and haemorrhagic (5% versus 11%) toxicities (Table IIa). Grade 3–5 haematological abnormalities were reported in 20% of patients taking imatinib at the lower dose versus 27% receiving the higher dose. A similar trend was observed in the Euro-Australasian trial [14],

Table IIb. Comparison of toxicities associated with imatinib therapy at doses of 400 mg/day and 800 mg/day in patients with advanced gastrointestinal stromal tumours in the b) Euro-Australasian study (Adapted from reference [13]).

Adverse event, n (%)	Imatinib 400 mg/day (n=470)	Imatinib 800 mg/day (n=472)	P-value ^a
Oedema	336 (71)	412 (87)	<0.0001
Anaemia	418 (89)	468 (98)	<0.0001
Rash	125 (27)	220 (47)	<0.0001
Nausea	229 (49)	286 (61)	<0.0001
Bleeding	51 (11)	105 (22)	<0.0001
Diarrhoea	226 (48)	268 (57)	0.0026
Dyspnoea	54 (11)	83 (18)	0.036
Pleuritic pain	240 (51)	160 (55)	0.053

^aadjusted for repetitive testing (Hommel Stet-up Procedure).

Table III. Dose reduction/interruptions due to adverse events associated with imatinib therapy at doses of 400 mg/day and 800 mg/day in patients with advanced gastrointestinal stromal tumours.

	Euro Australasian study [14]		North American study [13]	
	Imatinib 400 mg/day (n=473)	Imatinib 800 mg/day (n=473)	Imatinib 400 mg/day (n=330)	Imatinib 800 mg/day (n=333)
Dose reductions, n (%)	77 (16)	282 (60)		
Due to toxic effects, n (%)	60 (12)	213 (46)	52 (16)	192 (58)
Dose interruptions, n (%)	189 (40)	302 (64)		
Due to toxic effects, n (%)	135 (29)	235 (50)	124 (38)	198 (59)

in which grade 3–4 anaemia, fatigue, oedema, rash, diarrhoea, nausea, bleeding and dyspnoea were significantly more common with the 800 mg/day dose than with the 400 mg/day dose (Table IIb).

In the Euro-Australasian study, dose reductions (60% versus 16%) and treatment interruptions (64% versus 40%), including those due to toxicity, were more common with imatinib 800 mg/day than with imatinib 400 mg/day, respectively [14] (Table III). A similar trend was noted in the North American study.

Cardiotoxicity and imatinib treatment. Despite reports in 2006 of patients who developed CHF whilst under treatment with imatinib [38,39], a review of 942 patients with GIST enrolled in a phase III randomised controlled trial of imatinib could not identify an excess of cardiotoxicity and concluded that the possibility of imatinib-induced cardiotoxicity could not be excluded in only 0.2% of patients [40].

In a recent prospective analysis of 55 GIST patients, imatinib treatment was not associated with an increase in plasma N-terminal pro B-type natriuretic peptide (BNP) or troponine levels [41]. Based on these results the risk of developing cardiac toxicity with imatinib seems to be limited and these results do not support routine cardiac monitoring in all patients.

Thyroid dysfunction and imatinib treatment. As with sunitinib, abnormal thyroid function and hypothyroidism have been reported in patients with advanced GIST treated with imatinib [42,43]. In contrast to sunitinib, imatinib does not seem to have an effect in patients with normal thyroid function [44]. However, in thyroidectomised patients and in those with existing hypothyroidism, imatinib has been reported to increase daily thyroxine requirements [30,42]. Although routine screening of thyroid dysfunction in non-thyroidectomised patients receiving imatinib is not indicated, clinicians should be aware that these patients have a higher likelihood of increased levothyroxine replacement and should be monitored more

closely for elevations in thyrotropin indicating worsening hypothyroidism [42,43].

Other and rare AEs with imatinib. As with sunitinib, rare and unexpected AEs are being reported with increasing use of imatinib. A recent report has linked imatinib use with the development of changes in bone mineral metabolism in patients with CML and GIST [45]; 16 patients had low serum phosphate levels group (median serum phosphate level, 2.0 mg/dL) and eight patients had normal serum phosphate levels (>2.5 mg/dL) in the study. Patients in the low-phosphate group were receiving a higher dose of imatinib than patients in the normal-phosphate group. Both groups had high levels of phosphate excreted in the urine and markedly decreased serum levels of osteocalcin suggesting that imatinib may inhibit bone remodelling even in patients with normal serum phosphate levels.

In contrast to the case reports in CML patients, there are few reports of imatinib-induced hepatitis in GIST patients [46]. In the large multicenter trials with imatinib in GIST patients, grade 3–4 liver toxicity was observed in 2–4% [13,14]. In the large Euro-Australasian phase III study 3/942 patients died due to toxic hepatic events [14]. In the North American study 25/691 patients (3.6%) experienced grade 3–5 hepatic AEs and one high-dose patient died from infection combined with arrhythmia, liver failure, and confusion [13].

To date there has been only one report of tumour lysis syndrome in a patient with metastatic GIST who was treated with imatinib [47].

There have been reports of patients with CML treated with imatinib showing improvement in glycaemic control or regression of their diabetes [48,49]. Similar response has also been noted recently in RCC patients treated with sunitinib [50,51]. These cases suggest that RTKs may affect glucose metabolism. Blood sugar levels should therefore be monitored in these patients and doses of antidiabetic drugs adjusted as necessary. While there have not been any reports in GIST patients with diabetes, it is possible that such reports may yet emerge.

Close monitoring of patients receiving RTKs is essential to ensure emergent AEs are picked up and that patients are managed appropriately.

Influence of disease on toxicity profile

The type of malignancy for which patients are receiving treatment appears to have some influence on the toxicity profile of RTK inhibitors. Some differences in the incidence and severity of AEs have been noted between patients with mRCC and advanced GIST who received treatment with sunitinib. In patients who received second-line treatment with sunitinib in clinical trials, cardiotoxicity, hypothyroidism and bleeding events have been reported more commonly in those with mRCC than those with advanced GIST [24].

Similarly, differences have been noted between patients with CML and metastatic GIST treated with imatinib. In clinical trials of imatinib-treated cancer patients, headache, abdominal pain, haemorrhage, pleural effusion, pneumonia and flushing were more common in GIST patients than in patients with chronic CML. In contrast, musculoskeletal pain and related events were more commonly observed in patients with CML than in GIST patients [24].

These apparent differences in drug tolerability profiles between patients with different malignancies remain largely unexplained. Possible explanations may be that pre-treatment with cytokines in RCC patients might be an additional factor for developing thyroid dysfunction or that CML patients often have high tumour load, which may predispose to tumour lysis syndrome and/or hepatic failure.

Mechanisms by which RTK inhibitors cause adverse events

Imatinib and sunitinib both target similar receptors in GIST, the RTKs KIT and PDGFR- α . In addition, the two agents target other receptors. Imatinib also targets Bcr-Abl while sunitinib targets PDGFR- β , VEGFR-1, -2, and -3, FLT3, CSF-1R and RET. As the toxicity profiles of these RTK inhibitors have been determined, some typical class-specific AEs have emerged, and the mechanisms by which the RTK inhibitors cause these AEs have been postulated from their modes of action. The AEs observed will depend on the location of these receptors in tissue other than GISTs. An overview of the potential mechanisms underlying some of the most frequently occurring AEs associated with imatinib and sunitinib therapy is given below.

VEGFR inhibition

AEs that are believed to be due to VEGFR inhibition include hypertension [52,53], haemorrhage [52,54],

mucositis, skin toxicity, hand-foot syndrome, hypothyroidism [55–58] and fatigue [59].

Hypertension. The proposed mechanisms of hypertension associated with VEGF inhibitors are not yet fully understood, but include decreased production of nitric oxide (NO) in the wall of arterioles and other resistance vessels, reduced responsiveness of vascular smooth muscle cells to NO, an increased production of vasoconstricting stimuli, and microvascular rarefaction (reduced density of microvessels in tissues and organs) [52,59,60]. However, the effects of VEGF inhibition are thought to be very complex, suggesting that multiple factors are involved [52,59].

Hypothyroidism. VEGF plays a role in normal thyroid function and increased levels and enhanced expression of its receptors have been found in patients with Grave's disease and non-toxic goitres [55–58]. However, it is not definitively clear if VEGF inhibition directly causes thyroid dysfunction and whether this can lead to fatigue. Several theories have been proposed to explain the thyroid dysfunction caused by RTK inhibitors, including that suggested by Kamba and McDonald [52]. Based on animal studies, they proposed that regression of capillaries around thyroid follicles was responsible. Other theories suggest that inhibition of thyroid peroxidase leads to reduced production of thyroid hormone [30]; an unknown mechanism is responsible [27] or that sunitinib inhibits the thyroidal uptake of iodine [28]. De Groot et al. [42] suggested that imatinib-induced hypothyroidism involves stimulation of thyroxine (T4) and tri-iodothyronine (T3) clearance.

KIT inhibition

Inhibition of KIT has been associated with hypopigmentation of the hair (sunitinib) and skin (imatinib), and hair repigmentation (imatinib). This phenomenon is poorly understood.

Skin. Hypopigmentation of the skin has been reported in patients with advanced GIST treated with imatinib [2,61] and skin discoloration has been observed in patients with advanced GIST treated with sunitinib in clinical trials [12,19].

Both imatinib and sunitinib inhibit KIT, which plays a role in melanocyte development and survival [61], while stimulation of KIT affects pigment production [62,63]. The opposing effects on hair

pigmentation reported for the two drugs may be the result of differing action on KIT signalling. Alternatively, these effects could be due to their differing activity ranges, because sunitinib inhibits VEGFR as well as KIT and PDGFR [31].

PDGFR inhibition

AEs attributable to the inhibition of PDGFR include cardiotoxicity, skin reactions and facial oedema. In addition, an effect of imatinib on bone metabolism by PDGFR inhibition has been demonstrated in a recent study [64].

Cardiotoxicity. While the incidence of cardiotoxicity in association with sunitinib and imatinib treatment in patients with advanced GIST is unclear, both agents have been associated with cardiotoxicity as previously discussed.

Of the RTKs targeted by sunitinib, only PDGFRs are known to be expressed in cardiomyocytes but their inhibition has not been implicated in cardiotoxicity. This suggests that another target may be involved, and further investigation is warranted [65,66].

Imatinib inhibits Abl (Bcr-Abl), a tyrosine kinase not known to be involved in cardiomyocyte development and maintenance. However, studies in cultured mice and human cardiomyocytes suggested that imatinib is cardiotoxic, while Kerkela et al. showed that gene transfer of c-Abl protected cardiomyocytes from imatinib-induced cell death [38]. The mechanism postulated is that imatinib induces endoplasmic reticulum stress in cardiomyocyte mitochondria, which leads to the release of cytochrome C and expression of protein kinase C delta, resulting in cardiomyocyte death [38,66].

Recently, Chu et al. [23] proposed a similar mechanism for sunitinib and demonstrated that, in cultured rat cardiomyocytes, sunitinib activates caspase-9, leading to the release of cytochrome C and initiation of the apoptotic pathway in the mitochondria. They also demonstrated that the presence of hypertension increases cardiomyocyte apoptosis.

Maximising treatment benefit with RTKs

Adequate management of RTK-related AEs can allow patients to remain on treatment for long periods and help maximise the clinical benefit of targeted agents. The toxicity profile of each of the targeted agents approved for the treatment of GIST is well-defined and strategies to manage treatment-

related AEs are being refined. In addition, clinicians' familiarity with targeted agents is increasing and this experience is accompanied by the ability to manage treatment-related AEs more effectively. Effective therapy management involves optimisation of dose, maximising treatment duration and a proactive approach to the management of toxicities. Few management strategies for treating sunitinib-induced AEs have been validated in prospective trials, nonetheless, specific strategies for the management of some commonly presenting AEs with sunitinib treatment have been described, the majority in patients with metastatic renal cell carcinoma [67–70]. Management of AEs in patients with GIST will follow similar approaches. However, clinicians should keep in mind, as we have described earlier in this article, that the incidence and severity of the AEs may differ in patients with GIST and the degree of intervention will need to be adjusted accordingly. Patients should, therefore, be offered education and counselling by a care team experienced in the treatment of GISTs with RTK inhibitors.

In patients with discrete GISTs management may also include cytoreductive surgery if their tumours shrink to operable size while on sunitinib treatment. Since angiogenesis is a necessary step in wound healing, sunitinib with its multiple RTK inhibition is expected to impair surgical healing. In a retrospective analysis of 72 patients treated with sunitinib or imatinib before or after major surgery wound healing complications were not more common on sunitinib than on imatinib [71]. There are currently no recommendations for the optimal timing for administration and discontinuation of sunitinib to prevent surgical complications. Stopping sunitinib 8–10 days before performing non-urgent surgery and resuming at the first postoperative visit seems reasonable although no published guidelines exist.

Importance of optimising treatment exposure

Maintaining patients on RTK treatment is key to achieving tumour response and it is important to ensure that patients understand the importance of this at the outset. Improving adherence and limiting treatment interruptions will help to maintain satisfactory dosing levels [72], to ensure optimal blood drug levels are achieved for tumour response and to avoid 'flare-up' (defined as rapid re-growth of tumours after reversal of RTK inhibition resulting in increase of tumour-related symptoms) [73] thus optimising clinical outcomes. A pharmacokinetic/pharmacodynamic meta-analysis of phase II/III sunitinib studies has demonstrated that increased exposure to sunitinib in patients with advanced GIST is

associated with a higher probability of a partial response or complete response, longer progression-free survival, time to tumour progression, overall survival and greater reduction in tumour size [74]. In addition, studies with sunitinib have shown that discontinuation of treatment in patients with stable disease leads to 'flare-up' [75]. NCCN guidelines recommend these patients should be maintained on RTK treatment until disease progression [4].

Suggested dose modification strategy

Based on individual safety and tolerability, dose modifications in steps of 12.5 mg can be undertaken from the standard dose of 50 mg/day on schedule 4/2. Patients with symptoms of 'flare-up' in the two weeks off-treatment period are candidates for continuous dosing, for example 37.5 mg/day. Since 'flare-up' can occur in about 10% of patients treated with sunitinib on the intermittent schedule 4/2, imaging studies should be performed at the end of a treatment period rather than during or at the end of a rest period [75]. The behaviour and status of the disease should be taken into consideration when dose modifications are planned. When considering dose modifications physicians should be aware of a clear exposure-response relationship, which has been demonstrated in both RCC and GIST patients treated with sunitinib [74,76].

Conclusion

The RTK inhibitors imatinib and sunitinib represent a major advance in the treatment of advanced GIST. Patients usually require RTK therapy over long periods and, therefore, chronic AEs associated with their use may become a factor in patient acceptability and compliance.

Clinicians need to be familiar with the toxicity profiles of imatinib and sunitinib. They should be vigilant in monitoring patients for AEs such as CHF and hypothyroidism, which appear to be more common than previously reported, as well as more unexpected toxicities such as tumour lysis syndrome, whose mechanisms are not yet well understood. Clinicians should also be aware that individual patient risk factors may influence the incidence and severity of AEs.

AEs in cancer patients may be related to both the disease and its treatments. Patient involvement and education are the keys to managing expectations and improving treatment outcomes.

Imatinib and sunitinib are, generally, well tolerated with known and manageable AE profiles. Therapy management with sunitinib can maximise

treatment benefits can be maximised by risk assessment before treatment commences and the proactive management of AEs when they occur. This will enable patients to continue sunitinib treatment with minimal interruption and maintain satisfactory doses thus ensuring that blood drug levels are maintained at optimum levels for tumour response and to avoid 'flare-up' of disease.

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