Pharmacological management of gastrointestinal stromal tumours: an update on the role of sunitinib

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The efficacy and tolerability of the receptor tyrosine kinase inhibitor, sunitinib malate, have been demonstrated in phase I–III clinical trials of patients with imatinib-resistant or imatinib-intolerant gastrointestinal stromal tumours (GIST) as well as in a worldwide expanded-access study and in a continuous daily dosing (CDD) trial. Tumour genotype may have a significant influence on the activity of sunitinib in patients with imatinib-resistant GIST. Sunitinib activity was observed across different GIST genotypes and particularly in patients with wild-type and KIT exon 9 mutations (all relatively resistant to standard-dose imatinib) and in patients with secondary KIT exons 13 and 14 mutations. Adverse events with sunitinib were generally mild to moderate and easily managed by dose reduction, dose interruption or standard supportive measures. Treatment discontinuation can be avoided in most patients by close monitoring before and during treatment with appropriate adverse event management as necessary. The correlation between treatment exposure and clinical response is prompting the search for new approaches to treatment optimisation to ensure that patients derive maximum benefit from sunitinib therapy, including dose adjustments based on blood testing to ensure optimal drug exposure, and the use of the alternative CDD regimen to avoid treatment interruption.

Key words: adverse events, efficacy, gastrointestinal stromal tumours, KIT, resistance, sunitinib malate

introduction

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal tumour of the gastrointestinal tract. It presents most commonly in the stomach (50%) and can be found in the small intestine (25%), colon/rectum (5%–10%) and oesophagus (3%) [1].

The estimated worldwide incidence of GIST ranges from 6.8 per million population in the United States to 14.5 per million in Sweden [2]. Before the advent of targeted agents, median survival for patients with metastatic disease was 10–18 months [3]. Although GIST can occur at any age, the mean age of presentation is between 50 and 70 years [4].

Approximately 85%–90% of GISTs have activating mutations in stem cell factor receptor (KIT) [1, 5]. KIT contains 21 exons, but to date mutations have been reported within only exons 8, 9, 11, 13, 14, 17and 18. Approximately 5% of GISTs have activating mutations in the related gene encoding platelet-derived growth factor receptor alpha (PDGFRa) [6–8]. KIT and PDGFRa mutations are mutually exclusive: GISTs that have KIT mutations do not have PDGFRa mutations and vice versa [1]. A small number of GISTs (5%–10%) have neither KIT nor PDGFRa mutations (wild type) [1, 7].

Imatinib mesylate (Glivec®; Novartis Pharma, Basel, Switzerland) selectively inhibits KIT and PDGFR-α and was the first receptor tyrosine kinase (RTK) inhibitor approved for the treatment of adult patients with KIT-positive unresectable and/or metastatic malignant GIST. It is now considered the standard first-line treatment in these patients [9]. However, ~10% to 15% of GIST patients show primary resistance to imatinib [10, 11], 50% of patients develop secondary imatinib resistance within 2 years [11, 12], while 4% of patients are intolerant to imatinib therapy [13].

Sunitinib malate (SUTENT®; Pfizer, New York, NY) has been approved multinationally for the treatment of GIST after disease progression on or intolerance to imatinib, as well as for the treatment of advanced renal cell carcinoma (RCC). Sunitinib is 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, colony-stimulating factor 1 receptor and glial cell line-derived neurotrophic factor receptor (REarranged during Transfection) [14–19] and has direct antitumour and antiangiogenic activities.

A number of strategies can be employed to optimise treatment benefit with sunitinib. These include proactive adverse event (AE) management, dose adjustment and/or alternative dosing regimens; in the future, genetic testing may be of use to guide treatment with sunitinib. This review discusses the optimal use of sunitinib in advanced/metastatic GIST, reviews recent clinical data for sunitinib in this
indication and examines current and potential future approaches to GIST management.

**sunitinib efficacy**

**phase I/II clinical study**

A phase I/II, nonrandomised, open-label, dose-escalating study evaluated the safety, tolerability and pharmacokinetics of sunitinib in patients (N = 97) with imatinib-resistant metastatic GIST [20]. Sunitinib 50 mg/day was identified as the maximum tolerated dose and schedule 4/2 (4 weeks on treatment, 2 weeks off treatment) was chosen to maximise duration of sunitinib exposure. This treatment schedule moved forward into the phase II setting.

Partial responses (PRs: at least a 30% decrease in the sum of largest diameter (LD) of target lesions, taking as reference the baseline sum LD) by RECIST were confirmed in seven patients (7%) and 28 (29%) had stable disease (SD: less than a 30% decrease in the sum of largest diameter (LD) of target lesions, taking as reference the baseline sum LD, and less than 20% increase of the sum of largest diameter (LD) of target lesions, taking as reference the smallest sum on study) for ≥6 months. The overall median time to tumour progression (TTP) was 34 weeks (95% confidence interval [CI] 22.0–46.0 weeks). At the close of the study, 36 patients were still on treatment and were eligible for enrolment in a continuation protocol.

These findings showed that sunitinib has clinical activity in patients with imatinib-resistant GIST.

**phase III clinical study**

The efficacy of sunitinib demonstrated in the phase I/II study was confirmed in a phase III, multicentre, randomised, double-blind, placebo-controlled study of sunitinib in patients with advanced GIST with documented imatinib resistance or intolerance [21]. A total of 312 patients were randomly assigned 2 : 1 to receive sunitinib 50 mg/day (n = 207) or placebo (n = 105) on schedule 4/2. The trial was unblinded early when a planned interim analysis showed significantly longer TTP in the sunitinib group compared with the placebo group; all patients were allowed to cross over to open-label sunitinib.

Median TTP was 27.3 weeks (95% CI 16.0–32.1) in patients receiving sunitinib and 6.4 weeks (95% CI 4.4–10.0) in those receiving placebo [hazard ratio (HR) 0.33; 95% CI 0.23–0.47; P < 0.0001; Figure 1A]. Median progression-free survival (PFS) was 24.1 weeks (95% CI 11.1–28.3) for sunitinib and 6.0 weeks (95% CI 4.4–9.9) for placebo (HR 0.33; 95% CI 0.24–0.47; P < 0.0001).

Long-term survival data of this trial (N = 361) were analysed using a novel statistical method, the rank-preserving structural failure time (RPSFT) method, to account for bias introduced by patients crossing over from placebo to active treatment [22]. The RPSFT statistical analysis method was proposed by Robins and Tsiatis [23] and is a nonparametric model that produces a randomisation-based effect estimator. The model identifies survival differences that would have been observed if all subjects had remained on protocol.

In the sunitinib group, median overall survival (OS; 73.9 weeks; 95% CI 61.3–85.7) was twice that in the placebo group (35.7 weeks; 95% CI 25.7–49.8; P < 0.001; Figure 1B). In comparison, OS analysis using the traditional Kaplan–Meier method [21] revealed no statistically significant differences in median OS between patients receiving sunitinib (73.9 weeks) and those receiving placebo (64.9 weeks; 95% CI 45.7–96.0; P = 0.161; Figure 1B).

Results of an analysis of the soluble KIT (sKIT) levels in patients receiving sunitinib in this phase III trial indicate that after two cycles of sunitinib treatment, circulating sKIT levels appear to act as a surrogate marker for clinical outcome (TTP) in GIST patients [24]. Patients with decreased levels at the end of cycle 2 had a median TTP of 34 weeks versus 16 weeks for patients with increased levels (HR = 0.73; 95% CI 0.63–0.86; P = 0.0002). Further studies are warranted.

**GIST expanded-access study**

In an ongoing, open-label, expanded-access study [25], patients who are ineligible to participate in sunitinib clinical trials or for whom sunitinib is unavailable before regulatory approval in their country are given access to sunitinib. The study has allowed the collection of broad safety and efficacy data from a large number of GIST patients. Sunitinib (50 mg/day) is administered (schedule 4/2) to patients with advanced GIST in whom prior imatinib therapy had failed.

As of December 2007, 1126 patients had been enrolled with an intention-to-treat population (ITT; i.e. patients who...
received at least one dose of sunitinib) of 1117. The ITT population was followed up for a median of 51 weeks (range 0.1–159). The estimated median TTP was 41.0 weeks (95% CI 36–47). A total of 564 (50%) patients were still alive at the time of data cut-off, and median OS was estimated at 75.0 weeks (95% CI 68–84), i.e. better than in the pivotal trial, which is a rare situation in oncology. These results confirm the long-term survival benefit of sunitinib treatment in a broader population than was included in the original clinical trials.

In subgroup analyses, age ≥65 years, lower prior imatinib dose (≤400 mg) and Eastern Cooperative Oncology Group performance status of one or less favoured longer OS. Therefore, these parameters may be important prognostic factors affecting the clinical outcome in this patient population, but further studies are required to confirm this.

**continuous-dosing study**

The efficacy of sunitinib was further demonstrated in a study that evaluated the safety and efficacy of continuous daily dosing (CDD) of sunitinib 37.5 mg in patients with advanced GIST after failure of imatinib [26].

In this open-label, multicentre, phase II trial, 60 of 61 patients were randomly assigned 1:1 to receive sunitinib 37.5 mg once daily either in the morning (a.m.) or evening (p.m.). The primary end point was clinical benefit rate (CBR), defined as the percentage of patients with complete response (CR), PR or SD ≥24 weeks as per RECIST. Secondary end points included objective response, PFS, safety/tolerability measures, pharmacokinetic parameters and plasma levels of biomarkers. Investigator-assessed efficacy and safety data obtained from this study and the earlier phase III trial were compared informally.

As of March 2008, the estimated median PFS was 34.0 weeks (95% CI 25–59); overall CBR was 53% (n = 32), including 12% of patients (n = 7) with PR and 42% (n = 25) with SD ≥24 weeks. Median OS was 107 weeks (95% CI 72 to not yet calculable). These efficacy results were comparable to those obtained from the phase III trial and they demonstrate that in this patient population, CDD of sunitinib at 37.5 mg has comparable efficacy to sunitinib 50 mg/day on schedule 4/2 and appears to be an effective alternative dosing strategy.

Analysis of data from this study [26] showed a correlation between plasma levels of biomarkers and sunitinib treatment; plasma levels of vascular endothelial growth factor increased steadily with sunitinib treatment, while levels of soluble vascular endothelial growth factor receptor (sVEGFR)-2 and sVEGFR-3 decreased over time. In addition, reductions in plasma sKIT levels from baseline appeared to correlate with longer OS, indicating that sKIT could act as a biomarker for clinical outcome in sunitinib-treated patients with GIST.

**impact of genotype on treatment response**

Studies with both imatinib and sunitinib have shown that the GIST genotype is an important predictor of the outcome of treatment [27–31]. These observations have led to the indication that the classification of GIST based on mutation status may be a useful prognostic indicator and raise the possibility of individualising RTK inhibitor therapy to maximise clinical outcome in patients with GIST.

GISTs with KIT exon 11 mutations are the most prevalent and appear to be sensitive to imatinib in most cases [27, 29]. In contrast, primary imatinib resistance is common in GISTs with KIT exon 9 mutations, PDGFR A D842V mutations or a wild-type genotype, and GISTs with these genotypes do not respond well to standard doses of imatinib (400 mg/day) [27, 29, 32]. Higher dose imatinib (800 mg/day) has shown benefit in some patients resistant to imatinib 400 mg/day [12, 33], particularly those with KIT exon 9 mutations [27]. Secondary imatinib resistance is linked to the development of acquired mutations of both KIT and PDGFR A, resulting in proteins with reduced biochemical sensitivity to this tyrosine kinase inhibitor [27, 32].

In the phase I/II sunitinib trial in patients with imatinib-resistant GIST [28], the three most common GIST mutational subtypes were sensitive to sunitinib. CBRS were 34% with KIT exon 11, 58% with KIT exon 9 and 56% with wild-type PDGFR A/KIT. GISTs with primary KIT exon 9 mutations had a higher PR rate compared with those exhibiting KIT exon 11 mutations, 37% versus 5%, respectively (P = 0.002).

PFS was significantly longer in patients with either a primary KIT exon 9 mutation (19.4 months, P = 0.0005) or a wild-type genotype (19.0 months, P = 0.0356) compared with patients with a KIT exon 11 mutation (5.1 months). Likewise, median OS was also significantly longer for patients with an exon 9 genotype (26.9 months, P = 0.012) or a wild-type KIT genotype (30.5 months, P = 0.0132) than for those with an exon 11 mutation (12.3 months) [28]. When considering these clinical outcomes, it is worth noting that patients with primary exon 11 mutations in KIT are more likely to have secondary mutations as they would have received imatinib for much longer than patients with exon 9 mutations or wild-type genotype who are predisposed to primary imatinib resistance [28]. In addition, these results are from a small group of selected patients and these observations would need to be confirmed in imatinib-naive patients with primary KIT exon 11 mutation and no secondary mutations.

Both in vitro and clinical results demonstrated that sunitinib was also effective for treatment of GISTs with secondary KIT mutations in exon 13 or 14 (which encode the ATP binding pocket of the RTK; CBR 65%) but was not as effective in patients with secondary KIT exon 17 or 18 mutations (which encode the activation loop; CBR 9%, P = 0.006) [28].

Because of these observations, treatment guidelines now indicate genotype testing (where available) as an aid to choosing the most appropriate therapy for individual patients in the first-line setting [9, 34].

**sunitinib safety**

The management of AEs is key to maintaining patients on therapy. The treatment–related AEs reported with sunitinib in clinical trials have been generally mild and reversible, with appropriate intervention allowing most patients to continue with treatment.

**phase I/II study**

The phase I/II [20] trial demonstrated the toxicity profile of sunitinib in patients with metastatic, imatinib-resistant GIST. The most commonly reported AEs of any cause included fatigue, diarrhoea, abdominal pain, skin discolouration, nausea,
constipation and hand–foot syndrome and were mainly grade 1–2. Treatment-related serious AEs experienced by more than one patient included haemorrhage (six patients, 6%), fatigue and hypertension (each three patients, 3%). Dose-limiting toxic effects included grade 3–4 nausea and vomiting, febrile neutropenia, asymptomatic lipase increase and fatigue.

The incidence of cardiovascular events with sunitinib was assessed in a retrospective analysis of all such events occurring in the 75 patients enrolled in this trial at one centre [35]. Researchers reported that 11% (n = 8) of patients experienced a cardiovascular event, 8% (n = 6) had congestive heart failure (CHF) and 47% (n = 35) became hypertensive (>150/100 mmHg). In addition, in patients treated with the approved dose of sunitinib (n = 36), 19% (n = 7) had a reduction in left ventricular ejection fraction (LVEF) of at least 15% and 6% (n = 2) had a reduction of at least 20%.

These results indicate a higher incidence of cardiotoxicity with sunitinib than was reported in the later phase III trial [21]. It is worth noting that the phase I/II trial enrolled patients who took sunitinib a longer time.

Table 1. Most common (>15%) non-haematological treatment-related AEs and haematological laboratory abnormalities in the phase III sunitinib trial [22]

| Table 1. Most common (>15%) non-haematological treatment-related AEs and haematological laboratory abnormalities in the phase III sunitinib trial [22] |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | Blinded phase                  | Open-label phase                | Blinded + open-label phases     |                                |
|                                | Sunctinib (n = 235)            | Placebo (n = 115)               | All patients (n = 247)          | Sunctinib (n = 241)           |
|                                | Grade 1/2, n (%)               | Grade 1/2, n (%)                | Grade 1/2, n (%)                | Grade 1/2, n (%)              |
| Most common (>15%) non-haematological treatment-related AEsa | Fatigue 71 (30) 19 (8) 24 (21) 2 (2) | 97 (39) 25 (10) | 88 (37) 25 (10) | Fatigue 71 (30) 19 (8) 24 (21) 2 (2) |
|                                | Nausea 63 (27) 3 (1) 14 (12) 2 (2) | 71 (29) 9 (4) | 82 (34) 6 (2) | Nausea 63 (27) 3 (1) 14 (12) 2 (2) |
|                                | Anorexia 47 (20) 0 (0) 5 (4) 1 (1) | 55 (22) 6 (2) | 64 (27) 2 (1) | Anorexia 47 (20) 0 (0) 5 (4) 1 (1) |
|                                | Dysgeusia 50 (21) 0 (0) 3 (3) 0 (0) | 54 (22) 1 (0.4) | 60 (25) 1 (0.4) | Dysgeusia 50 (21) 0 (0) 3 (3) 0 (0) |
|                                | Vomiting 39 (17) 1 (0.4) 7 (6) 1 (1) | 43 (17) 5 (2) | 51 (21) 3 (1) | Vomiting 39 (17) 1 (0.4) 7 (6) 1 (1) |
|                                | Yellow skin 42 (18) 0 (0) 5 (4) 0 (0) | 51 (21) 0 (0) | 49 (20) 0 (0) | Yellow skin 42 (18) 0 (0) 5 (4) 0 (0) |
|                                | Mucosal inflammation 34 (14) 2 (1) 0 (0) 0 (0) | 40 (16) 5 (2) | 44 (18) 4 (2) | Mucosal inflammation 34 (14) 2 (1) 0 (0) 0 (0) |
|                                | Hypertension 21 (9) 11 (5) 5 (4) 1 (1) | 36 (15) 19 (8) | 29 (12) 18 (7) | Hypertension 21 (9) 11 (5) 5 (4) 1 (1) |
|                                | Rash 35 (15) 2 (1) 6 (5) 0 (0) | 36 (15) 1 (0.4) | 43 (18) 3 (1) | Rash 35 (15) 2 (1) 6 (5) 0 (0) |
|                                | Stomatitis 36 (15) 1 (0.4) 1 (1) 0 (0) | 35 (14) 4 (2) | 42 (17) 3 (1) | Stomatitis 36 (15) 1 (0.4) 1 (1) 0 (0) |
|                                | Dyspepsia 34 (14) 1 (0.4) 1 (1) 0 (0) | 42 (17) 2 (1) | 43 (18) 1 (0.1) | Dyspepsia 34 (14) 1 (0.4) 1 (1) 0 (0) |
|                                | Headache 24 (10) 1 (0.4) 7 (6) 0 (0) | 43 (17) 3 (1) | 41 (17) 3 (1) | Headache 24 (10) 1 (0.4) 7 (6) 0 (0) |
|                                | Hand–foot syndrome 19 (8) 9 (4) 1 (1) 0 (0) | 44 (18) 13 (5) | 30 (12) 14 (6) | Hand–foot syndrome 19 (8) 9 (4) 1 (1) 0 (0) |
|                                | Asthenia 28 (12) 6 (3) 2 (2) 2 (2) | 28 (11) 12 (5) | 30 (12) 13 (5) | Asthenia 28 (12) 6 (3) 2 (2) 2 (2) |
|                                | Hair colour changes 20 (9) 0 (0) 2 (2) 0 (0) | 49 (20) 0 (0) | 37 (15) 0 (0) | Hair colour changes 20 (9) 0 (0) 2 (2) 0 (0) |
|                                | Haemoglobin 125 (55) 9 (4) 60 (52) 2 (2) | 71 (29) 4 (2) | 132 (55) 11 (5) | Haemoglobin 125 (55) 9 (4) 60 (52) 2 (2) |
|                                | Neutrophils 106 (45) 24 (10) 4 (3) 0 (0) | 58 (23) 16 (6) | 113 (47) 28 (12) | Neutrophils 106 (45) 24 (10) 4 (3) 0 (0) |
|                                | Platelets 86 (37) 9 (4) 3 (3) 0 (0) | 46 (19) 3 (1) | 90 (37) 10 (4) | Platelets 86 (37) 9 (4) 3 (3) 0 (0) |

aTreatment = sunitinib.
bFive 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).
cBased on the sunitinib arm over the entire study.
dPer-protocol population.

AEs, adverse events.

phase III study

In the phase III trial [21], sunitinib was generally well tolerated and AEs were manageable. The incidence of treatment-related AEs for the blinded, open-label and overall populations in this trial was recently presented in an updated analysis (n = 243, sunitinib; n = 118, placebo) [22]. Over the entire study, the most common non-haematological treatment-related AEs were fatigue (47%), diarrhoea (43%), nausea (36%), anorexia (28%) and dysgeusia (25%; Table 1). Fatigue (10%), hypertension (7%) and hand–foot syndrome (6%) were the most common treatment-related grade 3–4 AEs. As expected, a slightly higher incidence of non-haematological AEs was noted in patients who took sunitinib a longer time.

The incidence of treatment-related hypertension (all grades) was 19% over the whole study in patients receiving sunitinib, and the incidence of cardiac AEs of all grades was low (6%) [22]. The relationship between RTK inhibition and cardiac function has yet to be definitively established. However, a link between hypertension and VEGFR inhibition has been demonstrated.

All-grade treatment-related hypothyroidism was observed in 13% of patients.

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High rates of abnormal thyroid function have also been reported in patient subgroups in other studies of GIST patients treated with sunitinib [36, 37]. In addition, these reports have noted that the risk for hypothyroidism increased with the duration of sunitinib therapy, which was also observed in the updated results from the phase III trial. Hypothyroidism is easily manageable by thyroid replacement therapy [21, 36, 37].

Haematological laboratory abnormalities were more common in the sunitinib group than in the placebo group and were mainly grade 1–2. These included reduced levels of haemoglobin (59%, n = 143), neutrophils (59%, n = 141) and platelets (41%, n = 100). Haematological laboratory abnormalities are listed in Table 1.

Over the blinded and open-label phases of the study, dose interruptions were required in 43% (n = 103) of patients, 36% (n = 86) of which were due to AEs. There were dose reductions in 28% (n = 67) of patients on sunitinib [22].

**expanded-access study**

In the expanded-access study [25], 19% (n = 214) of patients discontinued treatment due to AEs and 46% (n = 510) due to lack of efficacy. Sunitinib dose reductions (for any reason) occurred in 42% (n = 465) of patients.

The most common treatment-related AEs of any cause were fatigue (42%, n = 465), diarrhoea (39%, n = 439) and nausea (28%, n = 315). 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). Grade 3–4 haematological abnormalities included neutropenia (7%, n = 82), thrombocytopenia (5%, n = 57) and anaemia (5%, n = 51).

All-grade treatment-related hypothyroidism occurred in 10% of patients.

Grade 3–4 cardiac-related events such as heart failure, CHF, myocardial infarction, pulmonary oedema and reduced ejection fraction all occurred in ≤0.6% of patients.

These results demonstrate that sunitinib is generally well tolerated in patients with imatinib-resistant or imatinib-intolerant advanced GIST who are ineligible for other sunitinib trials. The safety profile observed was consistent with that seen in phase I–III GIST trials with sunitinib.

**continuous-dosing study**

The AE profile from the CDD trial [26] was similar to that seen in the phase III trial. AEs necessitated dose reduction to 25 mg in 23% (n = 14) of patients and 3% (n = 2) of patients discontinued treatment due to AEs.

The most common non-haematological treatment-related AEs were diarrhoea (42%, n = 25), asthenia (37%, n = 22), fatigue (33%, n = 20) and nausea (27%, n = 16). There were no reports of grade 4 events among the AEs listed. Haematological laboratory abnormalities of any grade included anaemia (83%, n = 50), neutropenia (57%, n = 34) and thrombocytopenia (42%, n = 25). Grade 3–4 haematological laboratory abnormalities included neutropenia (15%, n = 9), anaemia (12%, n = 7) and thrombocytopenia (7%, n = 4). Toxic effects were comparable between a.m. and p.m. dosing and this dosing schedule achieved constant drug exposure without accumulation of sunitinib.

This study demonstrates that in patients with imatinib-resistant or imatinib-intolerant GIST, CDD of sunitinib at 37.5 mg results in a similar safety and tolerability profile as when administered at 50 mg/day on schedule 4/2 and appears to be a safe alternative dosing strategy in this group of patients.

**apparent differences in tolerability profile in RCC and GIST patients**

The tolerability profile of sunitinib appears to differ in patients with metastatic renal cell carcinoma (mRCC) and those with advanced GIST. Differences were also noted between treatment-naive and previously treated mRCC patients. These differences are evident in both the incidence and severity of some AEs. In clinical trials with sunitinib, fatigue, hypertension, cardiotoxicity, hypothyroidism and bleeding events have been reported more commonly in patients with cytokine-refractory mRCC than those with imatinib-resistant or imatinib-intolerant GIST.

In patients with imatinib-resistant or imatinib-intolerant GIST [21], grade 3 fatigue was reported in 5% (total all grade, 34%) of patients compared with 11% (28%) of patients with cytokine-refractory mRCC [38] and 2% (14%) of patients with treatment-naive mRCC [39]. Similarly, 3% (total all grade, 10%) of patients with imatinib-resistant or imatinib-intolerant GIST had grade 3 hypertension, compared with 6% (16%) and 2% (6%) of patients with cytokine-refractory and treatment-naive mRCC, respectively [21, 38, 39].

Decreases in LVEF of ≥20% below the lower limit of normal were reported in ~2% of sunitinib-treated patients with imatinib-resistant GIST. In patients with cytokine-refractory mRCC, 4% exhibited an LVEF below the lower limit of normal [40].

Hypothyroidism was observed in 13% of patients with imatinib-resistant or imatinib-intolerant GIST [22] and in 4% of patients with cytokine-refractory mRCC [39]. In addition, 2% of patients with cytokine-refractory mRCC had elevated thyroid-stimulating hormone levels [40]. However, subsequent reports of hypothyroidism in mRCC patients receiving sunitinib have reported rates of up to 85% [41].

The incidence of bleeding events was lower in sunitinib-treated patients with imatinib-resistant or imatinib-intolerant GIST in a phase III trial compared with cytokine-refractory mRCC patients enrolled in an uncontrolled study (18% versus 26%, respectively) [40].

The reasons for these apparent differences in tolerability profiles between patients with mRCC and those with advanced GIST are unclear. RCCs have been reported to produce cytokines responsible for several of the paraneoplastic syndromes associated with mRCC. Among these, interleukin-6, whose receptor is not inhibited by sunitinib, may be involved in the different susceptibility to the drug across tumour types [42].

**AE management**

Evidence from clinical trials in patients with GIST showed that AEs caused by sunitinib were generally grade 1–2 in severity.
and were managed by dose reduction, dose interruption and standard supportive medical treatment. In order for patients to derive the most benefit from sunitinib, proactive management of AEs and education of both physicians and patients are vital.

Before sunitinib treatment, it is important to carry out blood cell counts, thyroid function tests and blood pressure checks. In addition, patients should be counselled regarding possible AEs and best approaches to managing them effectively.

Cardiotoxicity experienced with sunitinib is reversible in most cases [35]. Both the United States and European Union prescribing information (summary of product characteristics) for sunitinib recommend close monitoring for clinical signs and symptoms of CHF, especially in patients with cardiac risk factors and/or history of coronary artery disease. Baseline and periodic evaluations of LVEF dysfunction should also be carried out for patients who have experienced cardiac events in the 12 months before receiving sunitinib [40].

In addition, clinicians should monitor thyroid function and treat with thyroid hormone replacement if necessary. Strategies for the management of the AEs most commonly reported with sunitinib treatment are described in Table 2.

**Approaches to therapy management**

As well as GIST mutational status and the satisfactory management of AEs, other factors can play a role in treatment outcomes with RTK inhibitors. Maintaining exposure to adequate levels of sunitinib and avoiding treatment interruptions are vital to maximising antitumour efficacy. In addition, the method of drug delivery may affect patient compliance with treatment and therefore lead to treatment interruption.

An exposure–response model with sunitinib demonstrated a link between exposure to sunitinib and the probability of PR, longer TTP and extended OS in patients with advanced RCC or mRCC [43]. Likewise, using a similar model, a meta-analysis of pharmacokinetic and efficacy data from three phase I–III clinical trials in patients with advanced GIST treated with sunitinib demonstrated that there was greater reduction in tumour size, higher probability of a PR or CR and longer PFS, TTP and OS with increased exposure to sunitinib [44]. The exposure–response relationship was not affected by race (Asian relative to Caucasian), gender or age.

In addition, studies have shown that in some patients, response to imatinib treatment diminishes over time due to increased elimination of active drug [45] and/or increased protein binding [46]. Therefore, dose adjustments based on blood levels of RTK inhibitors may be necessary to maintain adequate drug levels and prevent disease progression. Clinical experience with sunitinib indicates that some patients may need to be treated with higher or lower than approved doses on the intermittent dosing schedule (schedule 4/2) in order to achieve adequate blood levels. Further research is required in this area.

As well as ensuring adequate blood levels of drug while on treatment, avoiding treatment interruptions is essential to maintaining tumour response. A multicentre phase III study (N = 182) comparing continuous imatinib with interrupted imatinib beyond 1 year of treatment in patients with advanced GIST showed that interrupting treatment led to rapid disease progression in most patients [47]. There is currently no evidence to support the temporary discontinuation of treatment in patients with prolonged response to RTK inhibitor treatment. Indeed, current clinical recommendations are to continue treatment indefinitely in such patients [9].

Another important factor in maintaining patients on treatment and ensuring compliance is the method of treatment delivery. Sunitinib CDD offers an alternative dosing regimen that may allow patients who experience problems with schedule

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### Table 2. Recommended management of common AEs seen with sunitinib treatment

<table>
<thead>
<tr>
<th>AE</th>
<th>Recommended management</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>Evaluate for depression and consider antidepressant medication</td>
</tr>
<tr>
<td></td>
<td>Test for hypothyroidism and anaemia</td>
</tr>
<tr>
<td></td>
<td>Dose modification infrequent/rare (only if patients specifically request)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>No dose modification (unless in combination with another AE)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Blood cell counts, transfusion if needed, role of erythropoietin-stimulating agents unclear</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Consider antidiarrhoal medication if needed, dietary modification</td>
</tr>
<tr>
<td></td>
<td>Delay dose for grade 3/4 AE; consider dose reduction for grade 4 AEs</td>
</tr>
<tr>
<td>Oral changes (e.g. pain, glossodynia, taste disturbance, stomatitis ± ulcerations)</td>
<td>Delay or reduce dose for grade 3 AE</td>
</tr>
<tr>
<td>Skin/hair issues (e.g. hair/skin discolouration, dermatitis)</td>
<td>Advise patients about possible changes in skin and hair pigmentation</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>Use hand and foot care products and pain medication; decrease pressure on affected areas</td>
</tr>
<tr>
<td></td>
<td>Delay dose for painful callouses (dose reduction rare; sometimes implemented after patients have received one additional cycle)</td>
</tr>
<tr>
<td></td>
<td>Evening sunitinib dose may decrease symptoms as maximal plasma concentration will be achieved during the night</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Address unstable hypertension</td>
</tr>
<tr>
<td></td>
<td>Increase existing antihypertensive treatment doses</td>
</tr>
<tr>
<td>Nonfebrile neutropenia or thrombocytopenia</td>
<td>Blood cell counts</td>
</tr>
<tr>
<td></td>
<td>Delay dose if grade 3 AE persists after 2-week off-treatment period; reduce dose if persistent</td>
</tr>
<tr>
<td>LVEF dysfunction</td>
<td>Interrupt and/or reduce dose if LVEF is &lt;50% and &gt;20% below baseline</td>
</tr>
<tr>
<td></td>
<td>Discontinue sunitinib in the presence of congestive heart failure symptoms</td>
</tr>
</tbody>
</table>

Based on information from the SUTENT® SmPC [40], clinical trial reports and expert opinion.

AEs, adverse events; LVEF, left ventricular ejection fraction; SmPC, summary of product characteristics.
4/2 dosing to continue treatment. Although there have been no direct comparative trials, this regimen has been shown to have similar efficacy to schedule 4/2 [26].

conclusions

Sunitinib has demonstrated clinical benefit in patients with unresectable and/or metastatic GIST resistant or intolerant to imatinib. Use of sunitinib in a broader population than the phase I–III clinical trials has confirmed the prolonged OS benefit of this treatment.

Tumour genotype has a significant influence on the activity of sunitinib in patients with imatinib-resistant GIST. Sunitinib activity was observed in patients with wild-type and KIT exon 9 mutations (all of which are relatively resistant to imatinib), in addition to KIT exon 11 mutations. Activity was also observed in patients with secondary KIT mutations in exons 13 and 14.

The tolerability profile of sunitinib was generally consistent across the phase I–III studies and expanded-access study. Reported AEs were generally mild to moderate in severity and could be managed by dose reduction, dose interruption or standard supportive medical treatments. Monitoring before and during treatment with appropriate intervention as necessary should avoid the need for treatment discontinuation in most patients.

New approaches to optimising treatment with sunitinib are needed in order to ensure that patients derive maximum benefit from treatment. This may involve dose adjustments based on blood testing to ensure optimal drug exposure and the use of the CDD regimen as an alternative to intermittent dosing on schedule 4/2. In addition, patients who have a response to sunitinib should be maintained on treatment without interruption.

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disclosures

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references

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26. George S, Blay JY, Casali PG et al. Continuous daily dosing (DDD) of sunitinib (SU) in pts with advanced GIST: updated efficacy, safety, PK and


