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Sunitinib

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Contents

Abstract

▲ Sunitinib and its active metabolite (SU012662) are selective inhibitors of multiple receptor tyrosine kinases associated with tumour growth and angiogenesis.

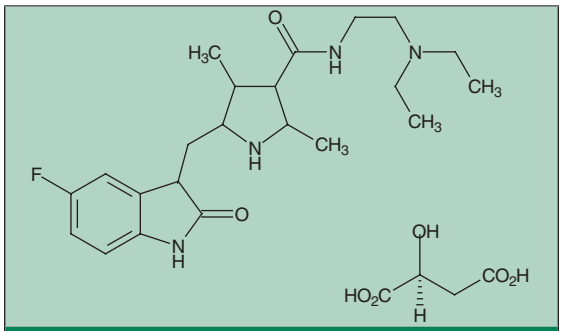
▲ The clinical efficacy of oral sunitinib has been demonstrated in patients with advanced gastrointestinal stromal tumours (GIST). In a phase III, randomised, double-blind, placebo-controlled, multicentre trial in patients with metastatic and/or unresectable GIST following unsuccessful imatinib therapy, the median time to tumour progression and median progression-free survival time were ≥4-fold longer in patients receiving sunitinib 50 mg/day than in those receiving placebo, in 6-week cycles consisting of 4 weeks of treatment followed by a 2-week rest period.

▲ Sunitinib also exhibited antitumour activity in patients with advanced renal cell carcinoma (RCC) following unsuccessful cytokine therapy. In two multicentre, single-arm, phase II clinical trials in patients with cytokine-refractory metastatic RCC, partial responses were reported in 40% and 43% of patients receiving sunitinib 50 mg/day for 4 weeks followed by 2 weeks without treatment in 6-week cycles; 27% and 22% of patients achieved stable disease for ≥3 months.

▲ Sunitinib was more effective than interferon-α as a first-line therapy in patients with metastatic RCC. In a large, well designed, phase III trial in previously untreated patients, progression-free survival was significantly longer in patients receiving sunitinib 50 mg/day in 6-week cycles (4 weeks of treatment followed by a 2-week rest period) compared with those receiving interferon-α 9MU three times weekly (47.3 vs 24.9 weeks).

▲ In general, sunitinib was well tolerated in patients with GIST and RCC, with adverse events usually being of mild or moderate severity.

Features and properties of sunitinib (SU011248; Sutent®)	
Indications	
Treatment of gastrointestinal stromal tumours (GIST) in patients with disease progression on, or who do not tolerate, imatinib therapy. Treatment of advanced renal cell carcinoma (RCC)	
Mechanism of action	
Inhibits multiple receptor tyrosine kinases including vascular endothelial growth factor receptor, platelet-derived growth factor receptor, stem cell factor receptor, Fms-like tyrosine kinase-3, colony stimulating factor type 1 and the glial cell-line derived neurotrophic factor receptor	
Dosage and administration	
Dose	50mg
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile of oral sunitinib 50 mg/day in patients with advanced malignancies after 4wk of treatment	
Mean maximum plasma concentration (C_{max})	Sunitinib: 72.2 ng/mL
	SU012662: 33.7 ng/mL
Mean area under the plasma concentration-time curve from 0 to 24 hours	Sunitinib: 1296 ng • h/mL
	SU012662: 592 ng • h/mL
Median time to C_{max}	Sunitinib: 8.5h
	SU012662: 6.5h
Elimination half-life	41–86h (single dose)
Most frequent adverse events	
GIST	Fatigue, diarrhoea, skin discolouration, nausea, anorexia
RCC	Fatigue, diarrhoea, nausea, stomatitis, dyspepsia, hypertension, hand-foot syndrome



Gastrointestinal stromal tumours (GIST) are relatively rare, with malignant cases estimated to affect 1500 people in the US annually.[1] Activating mutations in the genes encoding the receptor tyrosine kinases (RTKs) stem cell factor receptor (KIT) and platelet-derived growth factor (PDGF) receptor (PDGFR)-α are present in a large proportion of GIST patients.[2] Consequently, current first-line GIST therapy involves inhibition of tyrosine kinases, including KIT and PDGFR, with imatinib,[3] although initial and acquired resistance to therapy has prompted the need for more effective tyrosine kinase inhibitors.[4]

Renal cancer is the seventh most prevalent cancer among men and the eleventh among women in the US, with almost 40 000 new cases and >10 000 deaths estimated to occur in the US in 2006.[5] The standard treatment of advanced renal cancer has been immunotherapy-based for the last 20 years.[6] Historically, patients with progressive disease despite cytokine therapy had no further proven treatment options and exhibited a median survival of ≤1 year.[7] The 5-year survival rate of renal cancer patients with distant malignancy is <10%.[5] The von Hippel Lindau gene encoding a tumour suppressor protein involved in the regulation of hypoxia-inducible genes, such as vascular endothelial growth factor (VEGF) and PDGF, is frequently mutated or silenced in sporadic renal cell carcinoma (RCC).[8] VEGF and PDGF bind to tyrosine kinase receptors on endothelial cells and vascular pericytes and promote tumour angiogenesis.[9] Consequently, VEGF and PDGF signalling inhibitors have become a focus for RCC therapy.

Sunitinib malate (Sutent®)[1], hereafter referred to as sunitinib, is a selective inhibitor of multiple RTKs. Sunitinib was recently approved in the US where it is the only agent indicated for the second-line treatment of GIST and offers another treatment option in patients with advanced RCC. This article reviews the pharmacological properties of sunitinib and its efficacy and tolerability in patients with metastatic or unresectable GIST following unsuccessful imatinib therapy, and in patients with metastatic RCC.

1. Pharmacodynamic Profile

This section provides a brief overview of the pharmacodynamic properties of oral sunitinib. The pharmacodynamic effects of the drug have been reported in patients with RCC,[9-12] GIST[12-15] and other advanced malignancies[16-19] (n = 7–97). Some trials used the approved regimen of sunitinib 50 mg/day for 4 weeks followed by a 2-week rest period;[9,10,16,17] patients received a variety of regimens in other trials.[13,15,18,19] Additional data from one of these trials[9] are presented in an abstract;[10] further results from this trial[9] are presented in section 3. Some of the data are available only as abstracts and/or posters.[10,13-18,20,21]

Mechanism of Action

- Sunitinib is a potent inhibitor of multiple RTKs, through which its antitumour and antiangiogenic activities are mediated. Target RTKs include PDGFR-α and -β, VEGF receptors (VEGFR-1, VEGFR-2 (Flk-1/KDR) and VEGFR-3), KIT, Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor type 1 (CSF-1R) and the glial cell line-derived neutrophic factor receptor (RET).[22] In *in vitro* studies, sunitinib and its active metabolite (SU012662) have shown similar affinity for the RTKs PDGFR-α and -β, VEGFR-2 and KIT.[23]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Antitumour and Antiangiogenesis Effects

● Numerous studies have investigated the activity of sunitinib in murine models. In murine xenograft models of various human cancers, sunitinib exhibited antitumour activity causing tumour regression (13–62%) and growth inhibition (11–93%).[24] Phosphorylation of the sunitinib targets VEGFR-2 and PDGFR-β (critical mediators of tumour angiogenesis) within tumour xenografts was selectively inhibited by sunitinib treatment.[24] Similarly, in athymic mice with established human small-cell lung cancer xenografts[25] or FLT3-internal tandem duplication tumour xenografts,[26] sunitinib caused tumour growth inhibition or regression, and inhibited the phosphorylation of FLT3,[26] KIT and PDGFR-β.[25]

● Sunitinib significantly reduced levels of phosphorylated PDGFR-β (representative of active PDGFR-β) only in tumour biopsies of patients with metastatic, imatinib-resistant GIST for whom treatment resulted in clinical benefit (CB) [i.e. partial response (PR) or stable disease (SD) for >6 months].[14] Phosphorylated PDGFR-β levels were significantly ($p = 0.006$) reduced from baseline by 18% in patients exhibiting CB. In contrast, the increase from baseline in phosphorylated PDGFR-β levels in patients with progressive disease (PD) [SD for <6 months] was not significant (9.9%; $p = 0.06$).[14]

● The ability of sunitinib to inhibit VEGFR has been demonstrated in patients with GIST,[13,14] RCC[9,10] and other advanced malignancies[16-19] using plasma levels of VEGF or phosphorylated VEGFR as biomarkers of tumour growth inhibition. Sunitinib treatment increased VEGF levels (a typical response to angiogenesis inhibition and hypoxic conditions) in several studies in patients with imatinib-resistant GIST,[13] RCC[9,10] or advanced malignancies.[16-19] For example, after receiving sunitinib 50 mg/day for 4 weeks, 24 (44%) of 54 RCC patients exhibited a >3-fold increase from baseline in VEGF levels ($p < 0.001$).[10] During the following 2 weeks' no-treatment rest period, VEGF levels returned to near baseline.

● VEGFR-2 levels decreased during sunitinib treatment in patients with RCC,[9] GIST[14] or advanced malignancies.[16,17,19] For example, levels of phosphorylated VEGFR-2 were significantly ($p = 0.02$) reduced from baseline in tumour biopsies by 26.7% in GIST patients exhibiting a clinical response to sunitinib therapy (i.e. PR or SD for >6 months).[14] However, in patients with PD, VEGFR-2 phosphorylation increased significantly ($p = 0.02$) by 9.6%, highlighting a possible link between VEGFR-2 phosphorylation/inhibition status and clinical response.

● Plasma levels of soluble KIT (sKIT) decreased in patients with imatinib-resistant GIST receiving sunitinib 25–75 mg/day[13] and in RCC patients receiving sunitinib 50 mg/day.[10] In GIST patients, reductions in sKIT levels were evident only in patients who achieved reductions in unidimensional tumour size of at least 8%. Patients with tumours that did not regress exhibited no sKIT level reductions.[13] The decreased sKIT levels observed in RCC patients during sunitinib treatment did not correlate strongly with drug exposure.[10]

● Antiangiogenic properties of sunitinib have been demonstrated in the metastases of patients with advanced malignancies, including esophageal, colorectal and non-small-cell lung cancer[17,19] as well as RCC[17,19] and GIST.[19] Patients receiving sunitinib 50 mg/day exhibited a decrease in reference tumour blood flow of 20–85% after 2 weeks of treatment. However, three of the seven patients did not exhibit tumour responses after two cycles of therapy despite reduced tumour blood flow.[17] Also, intratumoral vessels were reported to progressively disappear in 6 of 22 (27%) evaluable patients following 1 week of sunitinib treatment.[19]

● Sunitinib increased endothelial and tumour cell apoptosis in patients with metastatic imatinib-refractory GIST 11 days after initiating therapy.[14] Tumour biopsies of patients with PR or SD for >6 months exhibited a 10- and 6-fold increase in endothelial and tumour cell apoptosis ($p < 0.05$ vs baseline). Biopsies from patients with PD exhibited negligible changes from baseline in apoptosis during therapy.

• Sunitinib reduced the metabolic rate of tumours in a proportion of patients with GIST[15] (83%, where stated[13]) or advanced malignancies (100%[17] and 41%[16]). In GIST patients receiving sunitinib, glucose metabolism was reduced significantly ($p < 0.001$) from baseline following 1 week of treatment, using calculated mean log maximum standardised uptake values.[15]

• Levels of regulatory T cells (Treg) decreased and the T helper cell (T_h) 1 : 2 bias typical of metastatic RCC (T_h1 suppression and T_h2 promotion) changed after sunitinib treatment in patients with cytokine-refractory, metastatic RCC.[11] Of ten evaluable patients, three exhibited a T_h1 bias and seven exhibited a T_h2 bias at baseline; however, after 28 days of receiving sunitinib 50 mg/day, six patients exhibited a T_h1 bias and four had reduced T_h2 responses.

• In addition, median levels of Treg cells expressing forkhead transcription factor (FoxP3; associated with reduced survival in several malignancies) decreased by 68% after 28 days of sunitinib therapy.[11] The relative changes in T_h1 bias correlated significantly ($p = 0.03$) with the extent of tumour reduction.

Other Effects

• In rats and monkeys, adrenal toxicity was reported with repeat sunitinib administration during studies of between 2 weeks and 9 months at exposures as low as 0.7 times the area under the plasma concentration-time curve (AUC) reported in clinical trials.[27] Changes in adrenal gland histology included haemorrhage, necrosis, congestion, hypertrophy and inflammation.

• In clinical trials, adrenal haemorrhage or necrosis was not evident in patients (n = 336) who received single or multiple cycles of sunitinib therapy.[27] However, across several clinical trials (n = 400), 11 patients with normal baseline adrenocorticotropic hormone (ACTH) stimulation results exhibited peak cortisol levels of 12–16.4 μ/dL at the final test (normal defined as >18 μ/dL) and one patient exhibited abnormal ACTH test results throughout sunitinib therapy despite normal baseline ACTH testing. No clinical evidence of adrenal toxicity was apparent during sunitinib therapy.

• Sunitinib may be associated with thyroid dysfunction.[12] Of 19 patients with GIST or RCC, seven patients (37%) had elevated thyroid-stimulating hormone (TSH) levels (>5 mIU/L) during treatment with sunitinib 50 mg/day (prospective analysis). Three of the 11 patients with RCC exhibited such increases within 6 weeks of receiving sunitinib therapy.

2. Pharmacokinetic Profile

Pharmacokinetic data were obtained from studies in healthy volunteers (n = 16–28)[28-30] and patients with advanced malignancies (n = 28),[19] with limited data available from patients with RCC (n = 63)[9] and GIST (n = 312).[31] Additional data from the manufacturer's prescribing information have also been included.[27] Some of the data are available only as abstracts and/or posters.[28-30]

• After administration of a single 50mg dose of oral sunitinib, maximum plasma concentrations (C_{max}) of both sunitinib and its active metabolite SU012662 were reached a median 5 hours postdose in patients with advanced cancers.[19] Following a single dose of sunitinib 50mg, mean C_{max} values of sunitinib and SU012662 were 27.7 and 4.12 ng/mL and values for the mean AUC from time zero to 24 hours (AUC_{24}) were 420 and 63.6 ng • h/mL.[19] After 4 weeks of sunitinib 50mg once daily, mean C_{max} values were 72.2 and 33.7 ng/mL reached in 8.5 and 6.5 hours and AUC_{24} values were 1296 and 592 ng • h/mL for sunitinib and SU012662.[19]

• The prescribing information reports that sunitinib and SU012662 accumulated 3- to 4-fold and 7- to 10-fold during repeat administration in healthy volunteers, with steady-state plasma concentrations of both compounds reached within 10–14 days of starting sunitinib therapy.[27] Dose-proportional increases in C_{max} and AUC from time zero to infinity (AUC_∞) were also reported with sunitinib 25–100mg.[27]

• Patients with RCC,[9] GIST[31] and various other cancers[19] receiving sunitinib 50 mg/day maintained combined trough plasma concentrations of sunitinib

and SU012662 of 50–100 ng/mL during treatment periods, levels known to inhibit RTKs in preclinical mouse xenograft models.[24]

- The bioavailability of sunitinib and exposure of the active metabolite were not significantly affected when food was taken prior to administration in healthy volunteers.[28]
- Sunitinib and SU012662 are 95% and 90% plasma protein bound *in vitro*; sunitinib has an apparent volume of distribution of 2230L.[27]
- Metabolism of sunitinib occurs primarily via the cytochrome P450 (CYP) enzyme CYP3A4, producing the active metabolite SU012662 that accounts for 23–37% of the total exposure.[27]
- Sunitinib is eliminated predominantly via faeces (61%) and urine (16%) and has a total oral clearance of 34–62 L/h.[27] The terminal half-life of sunitinib in patients with advanced cancer ranged between 41 and 86 hours following oral administration of a single 50mg dose.[19]
- The pharmacokinetics of sunitinib do not appear to be affected by tumour type, age, sex or bodyweight. No data are available concerning the pharmacokinetics of sunitinib in paediatric patients.[27] Clinical studies have not been conducted in patients with impaired hepatic or renal function, although population pharmacokinetic analyses indicate no alteration in sunitinib pharmacokinetics in patients with creatinine clearances of 2.5–20.8 L/h (42–347 mL/min).[27]
- Coadministration of sunitinib with potent inducers of CYP3A4 such as rifampicin (rifampin) may reduce sunitinib exposure.[29] Healthy male volunteers experienced reductions in C_{max} (2.3-fold) and AUC_{∞} (4.7-fold) following a single 50mg dose of oral sunitinib administered in combination with multiple doses of rifampicin 600 mg/day.[29] In contrast, the C_{max} and AUC of SU012662 increased following concomitant administration of sunitinib and rifampicin (2.4- and 1.3-fold),[29] although combined (sunitinib and SU012662) C_{max} and AUC_{∞} were reduced by 23% and 46%.[27]
- Coadministration of the CYP3A4 inhibitor ketoconazole and sunitinib may increase sunitinib exposure.[30] In healthy male volunteers, mean sunitinib C_{max} and AUC values were significantly increased by 58% and 69% after coadministration of sunitinib 10mg and ketoconazole 400 mg/day (p-values not reported).[30] Despite decreases in mean C_{max} of 29% and AUC of 13% for SU012662,[30] combined (sunitinib and SU012662) C_{max} and AUC_{∞} values increased by 49% and 51%.[27]

3. Therapeutic Efficacy

Gastrointestinal Stromal Tumours (GIST)

Phase I/II Trials

The efficacy of oral sunitinib in patients with confirmed metastatic or unresectable GIST for which imatinib therapy was unsuccessful has been evaluated in an open-label, multicentre phase I/II trial, available as an abstract and poster.[32]

Trial eligibility criteria required patients (n = 97) to have ceased imatinib therapy at least 2 weeks before the start of the trial and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.[32] Median patient age was 53 years and 66% were male; patients discontinued imatinib because of disease progression (96%) or intolerance (4%). Patient responses to sunitinib were assessed using Response Evaluation Criteria in Solid Tumours (RECIST) and defined as complete response (CR), PR, SD or PD.

- During the phase I portion of the study, different dosing schedules were assessed. The treatment regimen of sunitinib 50 mg/day for 4 weeks followed by a 2-week rest period yielded the greatest number of responses and was implemented in the phase II phase of the trial.[32]
- During the phase I/II trial, sunitinib therapy showed clinical activity in patients with imatinib-refractory GIST.[32] Eight percent of sunitinib recipients exhibited a PR, 33% and 37% had SD for 6 weeks to 6 months or ≥6 months, and 22% experienced either SD for <6 weeks or PD.
- Sunitinib therapy was associated with an estimated median time to tumour progression and overall survival duration of 7.8 and 19.8 months.[32] Thirty-two patients with a PR or SD for >6 months entered

a continuation study in which they received ongoing sunitinib therapy.[32] After a median treatment duration of >1.5 years, 15 patients had no disease progression.

Phase III Trial

The efficacy of oral sunitinib has been compared with placebo in patients with progressive metastatic and/or unresectable GIST following unsuccessful imatinib therapy (due to disease progression or intolerance) in a large, randomised, double-blind, placebo-controlled, multicentre, phase III trial.[31] Additional data were obtained from the prescribing information.[27]

Patients received sunitinib 50mg (n = 207) or placebo (n = 105) once daily for 4 weeks followed by 2 weeks without treatment in each 6-week cycle.[31] Treatment continued until disease progression or an alternative reason for withdrawal.[27] Treatment of patients with progression became unblinded and placebo recipients were offered crossover to open-label sunitinib therapy.[31]

Baseline patient characteristics, including ECOG performance status (0–2) and prior imatinib exposure, were generally similar between sunitinib and placebo groups.[31] Overall, 70% of subjects were aged <65 years, 63% of patients were male and 88% were Caucasian.[27] The primary endpoint was time to tumour progression defined by RECIST.[31] Secondary endpoints included overall survival, progression-free survival and response rates.

- Patients with progressive metastatic and/or unresectable GIST treated with sunitinib had a significantly longer time to tumour progression than those receiving placebo.[31] Sunitinib improved the median time to tumour progression >4-fold compared with placebo (27.3 vs 6.4 weeks; $p < 0.0001$), with a hazard ratio (HR) of 0.33 (95% CI 0.23, 0.47) [figure 1].[31] Cox proportional hazard analysis indicated that sunitinib produced beneficial effects in patients in all evaluated subgroups (i.e. regardless of age, weight, time since GIST diagnosis or geographic region).[31]
- The median progression-free survival time of patients receiving sunitinib was significantly longer than in those receiving placebo (24.1 vs 6.0 weeks; $p < 0.0001$), with an HR of 0.33 (95% CI 0.24, 0.47) [figure 1].[31] PR, SD and PD were exhibited in 7%, 58% and 19% of sunitinib recipients compared with 0%, 48% and 37% of placebo recipients.[31]
- Overall survival was estimated to be longer in sunitinib than placebo recipients (HR 0.49; $p = 0.007$), although median overall survival has not yet been determined for either treatment group.[31]

Renal Cell Carcinoma (RCC)

Phase I/II Trials

Initial phase I dose-finding studies of sunitinib were conducted in patients with advanced solid tumours refractory to conventional therapy (including RCC where stated) [n = 28[19] and 23[18]]. Based on these studies, a sunitinib dosage of 50 mg/day was selected and implemented in phase II trials.

The clinical efficacy of oral sunitinib has been further studied in patients with cytokine-refractory metastatic RCC in two pivotal multicentre, single-arm, phase II clinical trials (n = 63[9] and 106[33]). Preliminary data from a phase II trial investigating the efficacy of sunitinib in patients (n = 60) with bevacizumab-refractory metastatic RCC [34] are also briefly discussed. Data are fully published[9,33] or available as an abstract.[34]

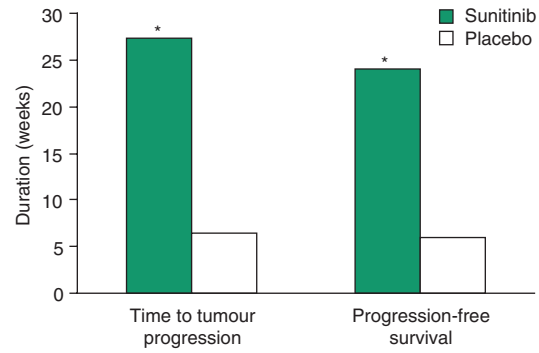


Fig. 1. Efficacy of sunitinib in patients with gastrointestinal stromal tumours (GIST). Median time to tumour progression and progression-free survival in a randomised, double-blind, placebo-controlled, multicentre trial in patients with progressive metastatic and/or unresectable GIST following unsuccessful imatinib therapy. Patients received sunitinib 50 mg/day (n = 207) or placebo (n = 105) for 4 weeks followed by 2 weeks without treatment in 6-week cycles; treatment continued until disease progression or withdrawal from the study.[31] * $p < 0.0001$ vs placebo.

Patient eligibility criteria for the two pivotal trials[9,33] included one previously unsuccessful cytokine (interferon-α, interleukin-2) regimen and an ECOG performance status of <2. Patients in the other trial[34] were required to have had disease progression (defined by RECIST) within 3 months of receiving bevacizumab therapy and a performance status of <2.

During each trial, patients received 6-week cycles comprising sunitinib 50mg once daily for 4 weeks followed by 2 weeks of no treatment.[9,33,34] Dose escalations[9] and reductions[9,33] were permitted depending on the absence or presence of adverse events, and treatment continued until disease progression or withdrawal criteria were met.[9,33]

At baseline, patients in the two pivotal trials[9,33] had a median age of 60[9] and 56[33] years, 68%[9] and 63%[33] were male, 87%[9] and 88%[33] had two or more sites of metastatic disease and 40%[9] and 19%[33] had received prior radiation therapy. Patient exclusion criteria included brain metastases and the occurrence of a significant cardiac event within 1 year prior to commencing the study.[9,33] In the trial in patients with bevacizumab-refractory metastatic RCC,[34] patients had a median age of 59 years, 92% had two or more sites of metastatic disease and 23% had previously received radiation therapy; exclusion criteria were not stated.

The primary endpoint in all trials was objective tumour response rate defined by RECIST[9,33,34] (specified as CR or PR in the two fully published trials[9,33]). Duration of response and survival were secondary[33] or unspecified[9] endpoints. Where stated, responses were assessed by an independent third-party imaging laboratory[33] and/or treating physicians.[9,33]

- Sunitinib showed antitumour activity in patients with metastatic RCC for whom conventional first-line cytokine therapy was unsuccessful, with the majority of patients experiencing measurable disease reduction.[9,33] In the smaller trial, 40% of patients exhibited a PR, 27% achieved SD for ≥3 months and 33% had PD or SD for <3 months (investigator assessments) or were not assessable.[9] Notably, eight patients with a PR continued to receive sunitinib and at the time of analysis were progression free over 21–24 months following therapy initiation. In this trial, median durations of response and survival were 8.7 and 16.4 months.
- The efficacy of sunitinib in patients with cytokine-refractory metastatic RCC was confirmed by data from the larger trial in which 43% of patients achieved a PR and 22% exhibited SD for ≥3 months; one patient achieved a CR (investigator assessments).[33] These data are supported by independent assessments of PR (34% of patients) and SD (achieved for ≥3 months by 29% of patients).
- The median duration of response, according to investigator assessment, was 10 months for the 46 patients with objective responses.[33] Thirty-four of the responders were still progression free at the time of analysis, including one with a complete response of >10 months' duration. Of the 36 responders identified by independent review, 10 had developed PD or had died at the time of analysis; median duration of response had therefore not been reached.
- The median progression-free survival was 8.1 and 8.3 months by investigator and independent assessments; the 6-month survival was 79% (overall survival had not been reached).[33]
- Preliminary results also suggest antitumour activity for sunitinib in patients with bevacizumab-refractory metastatic RCC.[34] Of the 32 evaluable patients, four exhibited a PR. Tumour reduction of some degree was demonstrated by 81% of patients.

Phase III Trial

Owing to the effective anti-tumour activity of sunitinib as a second-line therapy in clinical trials, the efficacy of sunitinib has also been compared with that of interferon-α, the standard treatment for advanced renal cancer, in previously untreated patients with metastatic RCC in a large, randomised, nonblind, phase III trial.[35] Data are available as an abstract.

Patients received oral sunitinib 50mg once daily in 6-week cycles (4 weeks of treatment followed by 2 weeks without treatment) [n = 375] or interferon-α 9MU via subcutaneous injection three times weekly (also in 6-week cycles) [n = 375].[35]

Baseline patient characteristics between treatment groups were well balanced (values were not reported); overall, patients had a median age of 60 years and 90% had previously had a nephrectomy.[35] The primary endpoint was progression-free survival, and secondary endpoints included objective response rate and overall survival. Endpoints were assessed by an independent third party and by investigator.

- Sunitinib demonstrated greater clinical efficacy than interferon-α as a first-line therapy in patients with metastatic RCC.[35] The median progression-free survival was significantly longer with sunitinib than with interferon-α treatment (47.3 vs 24.9 weeks; $p < 0.000001$), with a hazard ratio of 0.394 (95% CI 0.297, 0.521) [third-party independent assessment; investigator assessment was not reported].
- The objective response rate was also significantly greater in patients receiving sunitinib than in those treated with interferon-α, according to both third-party (24.8% vs 4.9%; $p < 0.000001$) and investigator (35.7% vs 8.8%; $p < 0.000001$) assessments. The number of patient deaths during treatment was numerically higher in the interferon-α group than in the sunitinib group (65 vs 49 deaths); statistical analysis was not reported.

4. Tolerability

Data concerning the tolerability of oral sunitinib 50 mg/day are available from the phase III trial in patients with metastatic and/or unresectable GIST following unsuccessful imatinib therapy[31] and the two phase II studies in patients with cytokine-refractory RCC[9,33] discussed in section 3. Some data were derived from the manufacturer's prescribing information,[27] including a pooled tolerability analysis of the two trials[9,33] in patients with RCC. Further tolerability data are available from studies in patients with GIST, including a phase I/II trial[36] and a retrospective analysis of a phase III trial.[12] Data from two studies in patients with advanced malignancies[19,37] and a phase II trial in patients with bevacizumab-refractory RCC, two of which are briefly discussed in section 3,[19,34] are also reported. Analyses were based on the per-protocol population in one trial.[31] Statistical analyses were not reported. Some data are available only as abstracts.[12,34]

GIST

- Oral sunitinib was generally well tolerated in patients with GIST, with adverse events usually being of mild to moderate severity.[31] Treatment-emergent adverse events were reported in 83% and 59% of sunitinib- and placebo-treated patients, with those considered serious occurring with an incidence of 20% and 5% in the respective treatment groups. Treatment discontinuation because of adverse events occurred in 9% and 8% of sunitinib and placebo recipients.[31]
- The most frequent treatment-emergent adverse events that occurred with at least a 5% greater incidence in sunitinib than placebo recipients included fatigue, diarrhoea, skin discolouration, nausea and anorexia (figure 2).[31] Grade 3 non-haematological treatment-emergent adverse events (there were none of grade 4 severity) included fatigue, hand-foot syndrome, asthenia, hypertension and diarrhoea (figure 2). Dose reductions were required in some sunitinib but in no placebo recipients (11% vs 0% of patients).[31]
- Haemorrhagic events occurred in 18% of GIST patients receiving sunitinib and in 17% of placebo recipients, with epistaxis the most commonly documented.[27] Grade 3 or 4 treatment-emergent intratumoral haemorrhages were documented only in sunitinib-treated GIST patients (3%).
- Treatment-emergent haematological adverse events (all grades) that occurred with a 5% greater frequency in GIST patients receiving sunitinib than in those receiving placebo included leukopenia (56% vs 5%), neutropenia (53% vs 4%), lymphopenia (50% vs 33%) and thrombocytopenia (41% vs 4%).[31] The numerical incidence of anaemia was similar in both sunitinib (62%) and placebo (60%) recipients.
- Treatment-emergent laboratory abnormalities (all grades) documented in ≥10% of GIST patients receiving sunitinib included raised liver function

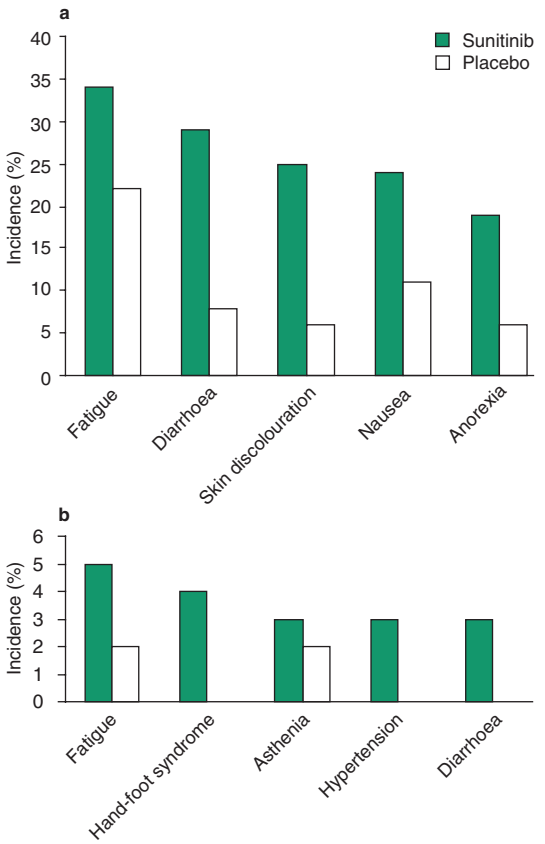


Fig. 2. Tolerability of oral sunitinib in patients with gastrointestinal stromal tumours (GIST). Incidence of adverse events of (**a**) all severities and of (**b**) grade 3 severity in sunitinib 50 mg/day (n = 202) and placebo (n = 102) recipients in a randomised, double-blind, placebo-controlled, multicentre trial in patients with metastatic and/or unresectable GIST following unsuccessful imatinib therapy.[31] Patients received once-daily sunitinib or placebo for 4 weeks followed by 2 weeks without treatment in 6-week cycles; treatment continued until disease progression or withdrawal from the trial.

tests, pancreatic enzymes and creatinine, as well as hypokalaemia and hypernatraemia.[27]

- In GIST patients, left ventricular ejection fraction (LVEF) values below the lower limit of normal were documented in 11% of sunitinib recipients and 3% of placebo recipients during treatment.[27] Sixty-four percent of the sunitinib-treated patients with low LVEF values (14 of 22) recovered with either no intervention or following additional treatment with antihypertensive or diuretic medication. Grade 3 LVEF reductions to <40% occurred in three sunitinib recipients (1%), and two of the three patients subsequently died.
- In a phase I/II trial in 79 patients with imatinib-refractory GIST, 26 (62%) of 42 patients who had normal thyroid function at baseline exhibited aberrant serum TSH levels after receiving multiple cycles of sunitinib therapy, each consisting of 2 or 4 weeks of sunitinib 50 mg/day followed by 2 weeks without treatment.[36] Moreover, hypothyroidism developed in 36% of the 42 patients after a mean of 50 weeks of sunitinib treatment, with the risk of developing hypothyroidism increasing with therapy duration.
- Furthermore, in a retrospective analysis of a phase III trial, hypothyroidism developed in 8 (57%) of 14 patients with GIST receiving sunitinib 50 mg/day for a median of 44 weeks.[12] Patients with GIST receiving sunitinib for 58–80 weeks exhibited TSH levels of up to 83 mIU/L and required hormone substitution.

RCC

- Adverse events reported in patients with RCC who received sunitinib were mostly of mild to moderate severity.[9,33] Treatment-emergent adverse events (of those with an incidence of ≥15% in either one of the two trials; all grades) included fatigue (38%;[9] 28%[33]), diarrhoea (24%;[9] 20%[33]), nausea (19%;[9] 13%[33]), stomatitis (19%;[9] 13%[33]), dyspepsia (16%[9,33]), hypertension (5%;[9] 16%[33]) and hand-foot syndrome (15%[33]).
- Grade 3 treatment-emergent adverse events (there were no grade 4 events) that occurred in at least 5% of RCC patients in either trial included fatigue (11%[9,33]), hand-foot syndrome (7%[33]), hypertension (2%;[9] 6%[33]), and stomatitis (2%;[9] 5%[33]).
- Dose reductions were reported in 22% and 35% of sunitinib recipients in the two trials,[27] commonly for fatigue (5 of 63 patients) and asymptomatic hyperlipasaemia or hyperamylasaemia (11 of 63 patients) where stated.[9]
- Haemorrhagic events occurred with an incidence of 26% in the RCC pooled analysis.[27] One patient

with bevacizumab-refractory RCC died from a treatment-related cerebral haemorrhage in a phase II trial.[34]

- Treatment-emergent haematological adverse events that occurred in at least 20% of patients in either RCC trial included lymphopenia (72%[9]), neutropenia (45%;[9] 42%[33]), anaemia (37%;[9] 26%[33]) and thrombocytopenia (18%;[9] 21%[33]). Hyperlipaseaemia was amongst treatment-related laboratory abnormalities and was reported in 24%[9] and 28%[33] of sunitinib-treated patients.
- In the pooled analysis, 15% of sunitinib recipients had LVEF values decrease below the lower limit of normal.[27] Four patients discontinued sunitinib treatment because of reduced cardiac ejection fraction in one of the studies.[9]

Other Malignancies

- Tumour necrosis developed in 6 of 22 evaluable patients with various advanced malignancies receiving sunitinib 50–150 mg/day in the phase I trial.[19] Tumour cavitations developed in four of the six patients; one GIST patient had a fatal peritoneal haemorrhage.[19]
- In patients (n = 24) with advanced malignancies who received sunitinib dosages approximately twice those associated with therapeutic concentrations, the corrected QT (QTc) interval was prolonged (Fridericia's correction; data were not reported).[37] However, the QT/QTc interval prolongations observed were no greater in severity than grade 2 (according to the Common Terminology Criteria for Adverse Events v3.0) and no patients experienced cardiac arrhythmia. The clinical relevance of these findings is unknown, but is likely to be influenced by individual patient susceptibilities and risk factors.

5. Dosage and Administration

Sunitinib is indicated for the treatment of patients with GIST or RCC and is available as an oral capsule. The recommended dosage is sunitinib 50mg once daily (with or without food) for 4 weeks followed by 2 weeks without treatment.[27] It is recommended that dosages are modified in increments of 12.5mg according to individual patient tolerability.[27]

Local prescribing information should be consulted for suggested modifications to dosage in patients receiving concomitant CYP3A4 inhibitor/inducer therapy or experiencing toxicity, and for information regarding contraindications, drug interactions and other precautions.

6. Sunitinib: Current Status

Sunitinib is approved in the US for the treatment of patients with GIST who have disease progression on, or do not tolerate, imatinib therapy and in patients with advanced RCC.[27]

In the EU, sunitinib has received conditional approval for use in patients with unresectable and/or metastatic malignant GIST after unsuccessful imatinib therapy due to intolerance or resistance and in patients with advanced and/or metastatic RCC after unsuccessful interferon-α or interleukin-2 therapy.[37]

Sunitinib is effective in the second-line treatment of metastatic and/or unresectable GIST, increasing the time to tumour progression >4-fold. It also shows efficacy in cytokine-refractory metastatic RCC, with partial response rates of >34%. In addition, sunitinib is more effective than interferon-α in the first-line treatment of metastatic RCC in terms of improvements in progression-free survival and response rate. Sunitinib is generally well tolerated.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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