JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010;40(3)194–202
doi:10.1093/jjco/hyp146
Advance Access Publication 7 November 2009

A Phase II Study of Sunitinib in Japanese Patients with Metastatic Renal Cell Carcinoma: Insights into the Treatment, Efficacy and Safety

Hirotsugu Uemura[1], Nobuo Shinohara[2], Takeshi Yuasa[3], Yoshihiko Tomita[4], Hiroyuki Fujimoto[5], Masashi Niwakawa[6], Soichi Mugiya[7], Tsuneharu Miki[8], Norio Nonomura[9], Masayuki Takahashi[10], Yoshihiro Hasegawa[11], Naoki Agata[12], Brett Houk[13], Seiji Naito[14] and Hideyuki Akaza[15]

[1]Department of Urology, Kinki University School of Medicine, Osaka, [2]Department of Urology, Hokkaido University Graduate School of Medicine, Sapporo, [3]Department of Urology, Akita University School of Medicine, Akita, [4]Department of Urology, Yamagata University School of Medicine, Yamagata, [5]Department of Urology, National Cancer Center Hospital, Tokyo, [6]Division of Urology, Shizuoka Cancer Center Hospital, Shizuoka, [7]Department of Urology, Hamamatsu University School of Medicine, Hamamatsu, [8]Department of Urology, Kyoto Prefectural University of Medicine, Kyoto, [9]Department of Urology, Osaka University Graduate School of Medicine, Osaka, [10]Department of Urology, University of Tokushima Graduate School, Tokushima, [11]Department of Urology, National Kyushu Cancer Center Hospital, Fukuoka, [12]Pfizer Japan Inc, Tokyo, Japan, [13]Pfizer Global Research and Development, La Jolla, USA, [14]Department of Urology, Graduate School of Medical Sciences, Kyushu University, Fukuoka and [15]Department of Urology, University of Tsukuba, Graduate School of Comprehensive Human Sciences, Tsukuba, Japan

For reprints and all correspondence: Hideyuki Akaza, Department of Urology, University of Tsukuba, Graduate School of Comprehensive Human Sciences, Tsukuba 305-8576, Japan. E-mail: akazah@md.tsukuba.ac.jp

Received June 23, 2009; accepted October 1, 2009

Objective: This study aims to assess the efficacy and safety of sunitinib in Japanese patients with metastatic renal cell carcinoma (RCC).

Methods: Fifty-one Japanese patients with prior nephrectomy, 25 treatment-naive patients (first-line group) and 26 cytokine-refractory patients (pretreated group) were enrolled in this phase II trial. Patients received sunitinib 50 mg orally, once daily, in repeated 6-week cycles (4 weeks on treatment, 2 weeks off). The primary endpoint was RECIST-defined objective response rate (ORR) with tumour assessments every 6 weeks via computed tomography or magnetic resonance imaging. Toxicity was assessed regularly. In the primary efficacy analysis of the intent-to-treat (ITT) population, ORR and 95% confidence interval were calculated based on independent review. Secondary time-to-event endpoints, such as progression-free survival (PFS), were estimated using the Kaplan–Meier method.

Results: In the ITT population, ORR was 48.0% in the first-line group (after a median 4 cycles), 46.2% in the pretreated group (5 cycles) and 47.1% overall, with median times to tumour response of 7.1, 10.7 and 10.0 weeks, respectively. Median PFS was 46.0, 33.6 and 46.0 weeks, respectively. The most common treatment-related grade 3/4 adverse events and laboratory abnormalities were fatigue (20%), hand-foot syndrome (14%) and hypertension (12%), decreased platelet count (55%), decreased neutrophil count (51%), increased lipase (39%) and decreased lymphocyte count (33%).

Conclusions: In Japanese patients with RCC, sunitinib is consistently effective and tolerable with similar risk/benefit as that in Western patients, though there was a trend toward greater antitumour efficacy and higher incidence of haematological adverse events in Japanese patients.

Key words: Japanese – phase II – renal cell carcinoma – sunitinib

INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 2–3% of all cancers (1,2) and 80–85% of cases of malignant kidney disease (1). The global incidence of RCC is increasing (3), with the highest rates in North America and Scandinavia (4). In Japan, there were an estimated 7400 persons diagnosed with RCC in 2002, up from 6360 persons in 1997, with crude incidence rates of 8.2 men and 3.6 women per 100 000 people (5).

Up to 30% of patients present with metastatic disease (6,7), and approximately 40% of patients treated for localized RCC eventually relapse (6,8). Until recently, cytokine therapy with interferon-alpha (IFN-α) and/or interleukin-2 (IL-2) had provided the mainstay of systemic RCC treatment, but with limited success and high corresponding rates of adverse events (9,10). More recently, increased understanding of RCC biology has led to the development of targeted agents that block proliferative, dysregulated tumour pathways and have demonstrated superior efficacy over cytokines and changed the RCC treatment paradigm (11,12).

Sunitinib malate (SUTENT®, Pfizer Inc., New York, NY, USA) is an oral, multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor receptors 1–3 and platelet-derived growth factor receptors α and β (13). Single-agent sunitinib showed unprecedented antitumour activity in two consecutive single-arm phase II trials of patients with cytokine-refractory metastatic RCC (14–16), demonstrating an objective response rate (ORR) of 33% (per independent, third-party, core imaging laboratory review), a median time to tumour progression (TTP) of 10.7 months, and a median overall survival (OS) of 23.9 months (as recently reported for the second phase II trial) (16). In addition, sunitinib subsequently demonstrated superior first-line efficacy over IFN-α, with significantly greater progression-free survival (PFS) and ORR (11 vs. 5 months and 47% vs. 12%, respectively; both $P < 0.001$) in an international, randomized phase III trial of 750 patients with metastatic RCC (17). Median OS was greater in the sunitinib group (26.4 months) vs. the IFN-α group (21.8 months).

These data have established sunitinib monotherapy as a standard of care for RCC treatment. Sunitinib is now approved multinationally for the treatment of first- and second-line advanced RCC. Here, we report the efficacy and safety results of the first Japanese phase II study of single-agent sunitinib in both treatment-naïve and cytokine-pretreated Japanese patients with metastatic RCC.

PATIENTS AND METHODS

Patient Population

The study population comprised patients aged ≥20 years with histologically proven RCC, with a clear-cell component and metastases; evidence of unidimensionally measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) (18) and prior nephrectomy. Other inclusion criteria included: Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; resolution of all acute toxic effects of prior therapy to ≤1 severity (classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 3.0); and adequate organ function. Patients with the following were excluded: any prior systemic treatment since RCC diagnosis (first-line population); any prior systemic therapy other than one cytokine-based regimen that could include multiple cytokines (pretreated population); prior treatment within 4 weeks of the start of study treatment; any secondary malignancy within the previous 5 years; uncontrolled hypertension; history of/known brain metastases; and cardiovascular disease. All patients gave written informed consent. This study was approved by the institutional review board at each participating centre and was conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice.

Study Design

This was a multicentre, open-label, non-randomized, single-arm, phase II study of sunitinib. Sunitinib was self-administered at a starting dose of 50 mg orally, once daily, in the morning, without regard to meals, in repeated 6-week cycles according to Schedule 4/2 (4 weeks on treatment followed by 2 weeks off).

Patients were monitored for toxicity, and doses were adjusted according to individual patient tolerance according to the protocol. Doses were reduced to 37.5 mg/day in cases of treatment-related grade ≥3 adverse events, and by an additional 12.5 mg/day if toxicities persisted to a minimum dose of 25 mg/day. Treatment was continued until one of the following occurred: disease progression; requirement for additional anticancer treatment; development of left ventricular systolic dysfunction; or treatment withdrawal.

Study Assessments

Patients were screened within 21 days prior to treatment initiation. Baseline evaluations included physical examination; ECOG PS; haematology; biochemistry; tumour assessment (scanned by computed tomography [CT] or magnetic resonance imaging [MRI]); 12-lead electrocardiography; and echocardiography or MUGA scan.

The primary efficacy endpoint was ORR, defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) according to RECIST (18). Tumour assessments were obtained every 6 weeks by investigators via CT or MRI scan with or without X-ray with response confirmed by an Extramural Review Committee (independent review). Secondary endpoints included PFS, TTP, duration of response, time to tumour response, and OS.

Safety and tolerability were assessed at regular intervals with adverse event monitoring, using NCI CTCAE version 3.0

to document adverse events and classify severity; haematology and biochemistry; body weight; vital signs; ECOG PS; 12-lead electrocardiography; and echocardiography or MUGA scan. Health-related quality of life was assessed using two measures from the EuroQol Group's EQ-5D self-report questionnaire, a population preference-based health state utility score (EQ-5D Index) and a visual analogue scale (EQ-VAS) for assessing a patient's overall health state (19–21).

Trough plasma concentrations of sunitinib, its active metabolite (SU12662) and total drug (sunitinib + SU12662) were assessed. Plasma samples for pharmacokinetic (PK) analysis were collected prior to treatment on days 1, 14 and 28 of cycle 1, days 1 and 28 of cycle 2, and day 28 of cycle 3.

Statistical Methods

In the primary efficacy analysis of the intent-to-treat (ITT) population, the ORR and 95% confidence interval (CI) were calculated for the first-line and pretreated populations based on independent review (the same analysis was performed for investigators' assessments). Sample sizes were calculated based on response rates for each population in which it was concluded that efficacy was confirmed if the lower limit of the 95% CI was greater than or equal to the threshold rate in each population. The thresholds were set at levels considered to be clinically ineffective for each population (5% for the pretreated population and 10% for the first-line population). Based on these assumptions, sample sizes of 26 and 25 patients were required for the pretreated and first-line populations, respectively, to provide a power of 80% with an alpha level of 2.5%. In the analysis of secondary endpoints, PFS, TTP and OS assessed by investigators were summarized using the Kaplan–Meier method (22). In the PK analysis, descriptive statistics were calculated for trough plasma concentrations of sunitinib, SU12662 and total drug.

RESULTS

Patients

As of February 2007 (time of data cutoff), 51 patients were enrolled at 12 sites in Japan and had completed at least four cycles of sunitinib treatment. The mean age was 56.6 years (range: 33–76) in the first-line population ($n = 25$) and 61.1 years (range: 34–77) in the pretreated population ($n = 26$). All patients had an ECOG PS of 0–1 at baseline. The most prevalent site of metastasis was the lung (82%). Baseline characteristics are summarized in Table 1.

In the second-line population, 22 patients (85%) had received previous treatment with IFN-α. The best responses to previous treatment were CR in one patient (4%) and PR in 11 patients (42%); 13 patients (50%) exhibited progressive disease. Cytokine-based treatment was discontinued because of tumour progression in 22 patients (85%), intolerance in two patients (8%) and other reasons in two patients (8%).

Table 1. Patient characteristics at baseline

Characteristic	First-line population ($n = 25$)	Pretreated population ($n = 26$)
Male, *n* (%)	11 (44.0)	21 (80.8)
Mean age, years (range)	56.6 (33–76)	61.1 (34–77)
≥65 years, *n* (%)	7 (28)	11 (42)
Mean weight, kg (range)	57.7 (40.0–77.5)	63.7 (42.1–92.4)
Median time since initial diagnosis, months (range)	2.69 (0.3–157.5)	16.69 (1.8–221.2)
ECOG PS, *n* (%)		
0	20 (80)	22 (85)
1	5 (20)	4 (15)
Common sites of metastases, *n* (%)		
Lung	19 (76)	23 (88)
Lymph nodes	8 (32)	11 (42)
Visceral organs	7 (28)	8 (31)
Bone	5 (20)	4 (15)
Prior cytokine-based therapy, *n* (%)		
IFN-alpha	–	22 (85)
IL-2	–	1 (4)
IFN-alpha + IL-2	–	2 (8)
IFN-alpha + IL-2 + tegafur-uracil	–	1 (4)

ECOG PS, Eastern Cooperative Oncology Group performance status; IFN, interferon; IL, interleukin.

Treatment and Disposition

At the time of analysis, patients in the first-line population had received a median of four cycles of treatment (range: 1–8) and patients in the pretreated population had received five cycles (range: 1–7). Eleven patients (44%) in the first-line population and nine patients (35%) in the pretreated population discontinued treatment. One patient in the pretreated population died due to tumour progression, which was considered unrelated to treatment. Sunitinib treatment and disposition by patient population are summarized in Table 2.

Efficacy

Based on independent review, ORR in the ITT populations was 48.0% (95% CI, 27.8–68.7) in the first-line population, 46.2% (95% CI: 26.6–66.6) in the pretreated population and 47.1% (95% CI: 32.9–61.5) in the overall population (Table 3). Identical ORR values were reported by the investigators. The lower confidence limit for ORR exceeded the threshold value for each population (10% for the first-line population and 5% for the pretreated population). Twelve patients in each population achieved a confirmed PR according to investigator assessment; one patient achieved a confirmed CR (and 11 patients achieved a confirmed PR) in the first-line population based on independent review (Table 3).

Median time to tumour response based on independent review was 7.1 weeks (95% CI: 4.0–10.1) in the first-line population, 10.7 weeks (95% CI: 4.0–16.0) in the pretreated population and 10.0 weeks (95% CI: 4.0–11.0) in the overall population, with similar data reported by the investigators (data not shown).

Table 2. Sunitinib treatment and disposition

	First-line population ($n = 25$)	Pretreated population ($n = 26$)
Median no. of treatment cycles (range)	4.0 (1–8)	5.0 (1–7)
Median duration of treatment, days (range)	148.0 (14–322)	196.0 (9–280)
Patients on treatment ≥6 months, *n* (%)	10 (40)	17 (65)
Median daily sunitinib dose, mg (range)	43.29 (30.4–50.0)	38.17 (27.7–50.0)
Treatment change due to adverse events, *n* (%)[a]	17 (68)	23 (88)
Discontinuations, *n* (%)	11 (44)	9 (35)
Owing to disease progression	6 (24)	4 (15)[b]
Owing to adverse event	5 (20)	4 (15)

[a]Treatment change includes dose reduction, temporary discontinuation, or extension of the defined off-treatment period.
[b]One of the four patients discontinued sunitinib treatment because of death due to tumour progression. Note: Adverse events referenced in this table were treatment-related.

Progressive disease during treatment with sunitinib (including 28 days after the completion of treatment) was documented by investigators in eight patients in both the first-line and pretreated populations (32% and 31%, respectively) including three patients who had PR on study, one patient and two patients, respectively. Of these three patients with PR, duration of response was 42.3 weeks for the first-line patient and 21.0 and 30.0 weeks for the pretreated patients.

Median PFS was 46.0 (95% CI: 46.0–NR), 33.6 (95% CI: 25.0–NR) and 46.0 (95% CI: 28.4–NR) weeks in the first-line, pretreated and overall populations, respectively (Figure 1; overall population not shown); PFS and TTP were identical. At the time of analysis, median OS had not been reached in either population.

Safety

All 51 patients experienced treatment-related adverse events, the majority of which were grade 1 or 2 in severity (Table 4). The most commonly reported treatment-related adverse events in the first-line population were anorexia (68%), skin discoloration (64%), diarrhoea (60%) and pyrexia (60%). In the pretreated population, the most commonly reported adverse events were skin discoloration (81%), fatigue (69%), anorexia (54%), dysgeusia (54%) and rash (54%).

The most common grade 3 adverse events in the first-line population were diarrhoea and hand-foot syndrome, each of which occurred in four patients (16%) and were manageable and reversible; the most common grade 3 adverse event in the pretreated population was fatigue, occurring in six patients (23%). No grade 4 or 5 treatment-related adverse events were reported in the first-line population, and in the pretreated population, one patient experienced grade 4 fatigue; however, this patient recovered and continued study treatment.

The most frequently reported laboratory abnormalities in the first-line population included decreased platelet count (96% of patients), white blood cells (84%), lymphocytes (84%) and neutrophils (72%), as well as increased lactate dehydrogenase (68%), aspartate aminotransferase (56%), lipase (60%), creatinine (56%) and alanine aminotransferase (52%; Table 4). Similar laboratory abnormalities were reported in the pretreated population, all occurring in >50% of patients except for increased creatinine, which occurred in 38%.

In the first-line population, the most common grade 3 laboratory abnormality was decreased platelet count, occurring in 12 patients (48%); the most common grade 4 abnormality was increased lipase, occurring in three patients (12%). In the pretreated population, grade 3 decreased neutrophils and platelets occurred in 15 (58%) and 12 patients (46%), respectively. No grade 5 laboratory abnormalities occurred in either patient population.

Table 3. Best RECIST-defined tumour response by independent review and investigator assessment

Response	First-line population ($n = 25$)		Pretreated population ($n = 26$)		Total population ($n = 51$)	
	Independent review	Investigator assessment	Independent review	Investigator assessment	Independent review	Investigator assessment
Objective response, % (95% CI)	48.0 (27.8–68.7)	48.0 (27.8–68.7)	46.2 (26.6–66.6)	46.2 (26.6–66.6)	47.1 (32.9–61.5)	47.1 (32.9–61.5)
Complete response, *n*	1	0	0	0	1	0
Partial response, *n*	11	12	12	12	23	24

CI, confidence interval.

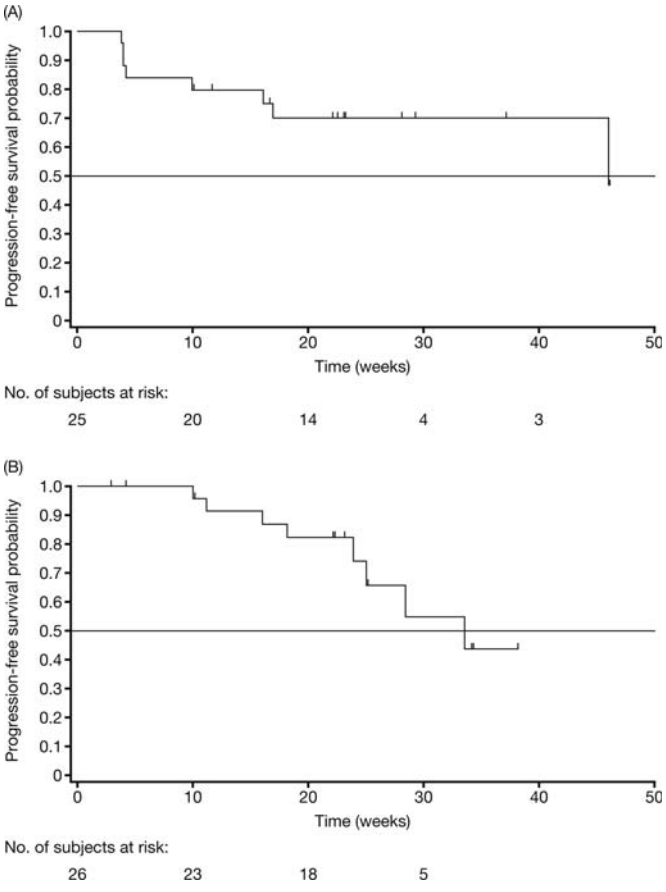

Figure 1. Kaplan–Meier estimates of progression-free survival in the (A) first-line and (B) pretreated populations.

Treatment changes (dose reductions, interruptions and/or extensions of off-treatment periods) owing to treatment-related adverse events were reported in 40 patients (78%); overall, 17 patients (68%) in the first-line population, and 23 patients (88%) in the pretreated population. Treatment changes owing to decreased platelet counts were reported in approximately 50% of patients.

QT-corrected interval prolongation occurred in two patients (4%) overall, but was not clinically significant and resolved without treatment changes. Reduced left ventricular ejection fraction (LVEF) was reported as a serious adverse event in one patient, but abated after treatment discontinuation.

Five patients (20%) in the first-line population and four patients (15%) in the pretreated population experienced treatment-related adverse events that led to discontinuation. The adverse events most commonly leading to discontinuation were hypertension and decreased LVEF, each reported in two patients (4%) overall. No discontinuations owing to haematological or biochemical laboratory abnormalities were reported.

Health-related Quality of Life

For the EQ-5D index score (data not shown), the range of mean change at each endpoint from baseline was from −0.1573 to 0.0375 in the first-line population and from −0.0974 to 0.0513 in the pretreated population. For EQ-VAS score (Figure 2), the range of mean change at each endpoint from baseline was from −12.35 to 2.71 in the first-line population and from −11.82 to 4.17 in the pretreated population. Both scores tended to decline during treatment with sunitinib and subsequently recovered during the off-treatment periods in both populations.

Pharmacokinetics

Median trough plasma concentrations of total drug reached therapeutic levels (>50 ng/ml) (23) on day 14 of cycle 1 in both populations, and levels were sustained throughout treatment during the dosing periods without clinically relevant differences in concentrations between populations. Median trough plasma concentrations of total drug on days 14 and 28 of cycle 1 were comparable to those observed on day 28 of cycles 2 and 3 (Figure 3).

Potential associations between body weight and systemic exposure (area under the plasma-concentration curve; AUC) to sunitinib, SU12662 and total drug were explored in Japanese and Caucasian subjects (Figure 4). The population for this analysis comprised 13 Western studies, one of which included Japanese subjects, and a Japanese study (25). No clear correlations between weight and exposure were observed in either population.

DISCUSSION

Results from this open-label, multicentre phase II trial demonstrated that sunitinib 50 mg, self-administered orally

Table 4. Treatment-related adverse events and laboratory abnormalities reported in >25% of patients in the first-line ($n = 25$) and pretreated ($n = 26$) populations

Adverse event	Maximum NCI CTCAE[a] Grade[b]				
	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	Total, *n* (%)
First-line population					
Anorexia	4 (16)	10 (40)	3 (12)	0	17 (68)
Skin discoloration	16 (64)	0	0	0	16 (64)
Diarrhoea	8 (32)	3 (12)	4 (16)	0	15 (60)
Pyrexia	9 (36)	6 (24)	0	0	15 (60)
Nausea	7 (28)	5 (20)	2 (8)	0	14 (56)
Stomatitis	8 (32)	4 (16)	1 (4)	0	13 (52)
Dysgeusia	8 (32)	4 (16)	0	0	12 (48)
Rash	11 (44)	1 (4)	0	0	12 (48)
Fatigue	4 (16)	5 (20)	3 (12)	0	12 (48)
Hand-foot syndrome	3 (12)	4 (16)	4 (16)	0	11 (44)
Hypertension	3 (12)	5 (20)	3 (12)	0	11 (44)
Vomiting	2 (8)	5 (20)	1 (4)	0	8 (32)
Face oedema	6 (24)	2 (8)	0	0	8 (32)
Malaise	6 (24)	1 (4)	1 (4)	0	8 (32)
Laboratory abnormality					
Decreased platelet count	7 (28)	3 (12)	12 (48)	2 (8)	24 (96)
Decreased white blood cell count	4 (16)	12 (48)	5 (20)	0	21 (84)
Decreased lymphocyte count	2 (8)	9 (36)	8 (32)	2 (8)	21 (84)
Decreased neutrophil count	4 (16)	4 (16)	8 (32)	2 (8)	18 (72)
Increased lactate dehydrogenase	11 (44)	5 (20)	1 (4)	0	17 (68)
Increased lipase	5 (20)	3 (12)	4 (16)	3 (12)	15 (60)
Increased creatinine	7 (28)	6 (24)	1 (4)	0	14 (56)
Increased aspartate aminotransferase	10 (40)	1 (4)	2 (8)	1 (4)	14 (56)
Increased alanine aminotransferase	8 (32)	2 (8)	3 (12)	0	13 (52)
Decreased haemoglobin	7 (28)	3 (12)	1 (4)	0	11 (44)
Increased amylase	6 (24)	3 (12)	2 (8)	0	11 (44)
Increased alkaline phosphatase	7 (28)	2 (8)	1 (4)	0	10 (40)
Increased bilirubin	3 (12)	3 (12)	1 (4)	0	7 (28)
Decreased calcium	5 (20)	2 (8)	0	0	7 (28)
Decreased phosphorus	0	1 (4)	6 (24)	0	7 (28)
Pretreated population					
Skin discoloration	20 (77)	1 (4)	0	0	21 (81)
Fatigue	8 (31)	3 (12)	6 (23)	1 (4)	18 (69)
Anorexia	9 (35)	5 (19)	0	0	14 (54)
Dysgeusia	12 (46)	2 (8)	0	0	14 (54)
Rash	13 (50)	1 (4)	0	0	14 (54)
Hand-foot syndrome	4 (15)	6 (23)	3 (12)	0	13 (50)
Hypertension	1 (4)	9 (35)	3 (12)	0	13 (50)
Pyrexia	4 (15)	6 (23)	1 (4)	0	11 (42)
Epistaxis	11 (42)	0	0	0	11 (42)
Stomatitis	6 (23)	3 (12)	1 (4)	0	10 (38)
Oedema peripheral	8 (31)	0	1 (4)	0	9 (35)
Eyelid oedema	8 (31)	1 (4)	0	0	9 (35)
Nausea	3 (12)	6 (23)	0	0	9 (35)
Cheilitis	6 (23)	2 (8)	0	0	8 (31)
Malaise	4 (15)	2 (8)	2 (8)	0	8 (31)
Face oedema	6 (23)	0	1 (4)	0	7 (27)
Diarrhoea	6 (23)	0	1 (4)	0	7 (27)
Pain in extremity	2 (8)	2 (8)	3 (12)	0	7 (27)
Laboratory abnormality					
Decreased platelet count	4 (15)	5 (19)	12 (46)	2 (8)	23 (88)
Decreased neutrophil count	3 (12)	3 (12)	15 (58)	1 (4)	22 (85)
Decreased white blood cell count	3 (12)	16 (62)	3 (12)	0	22 (85)
Increased lactate dehydrogenase	17 (65)	2 (8)	0	0	19 (73)
Increased aspartate aminotransferase	14 (54)	2 (8)	1 (4)	0	17 (65)
Increased lipase	1 (4)	3 (12)	10 (38)	3 (12)	17 (65)
Decreased lymphocyte count	2 (8)	5 (19)	5 (19)	2 (8)	14 (54)
Increased alanine aminotransferase	11 (42)	2 (8)	0	0	13 (50)
Increased amylase	7 (27)	2 (8)	3 (12)	0	12 (46)
Decreased haemoglobin	9 (35)	1 (4)	1 (4)	0	11 (42)
Increased creatinine	4 (15)	6 (23)	0	0	10 (38)
Increased bilirubin	3 (12)	5 (19)	0	0	8 (31)
Increased alkaline phosphatase	6 (23)	1 (4)	0	0	7 (27)

[a]National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
[b]No grade 5 adverse events or laboratory abnormalities were reported.

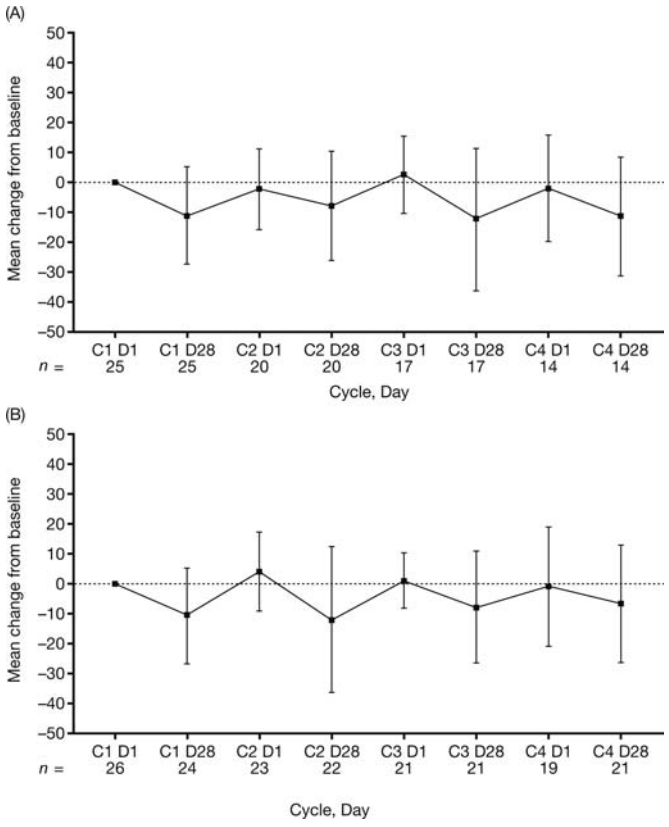

Figure 2. Mean change from baseline in EQ-VAS scores in the (A) first-line and (B) pretreated populations. EQ-VAS, EuroQol visual analogue scale; C, cycle; D, day (e.g. C1D1, cycle 1, day 1). Error bars represent standard deviations.

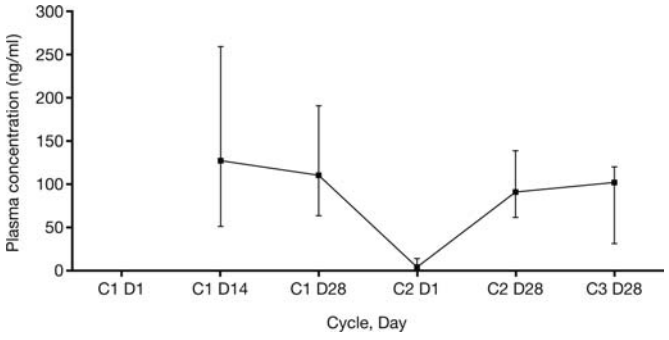

Figure 3. Median trough plasma concentrations of total drug (sunitinib + SU12662) for all patients receiving a sunitinib starting dose of 50 mg during cycles 1–3. Vertical bars represent ranges of median values. C, cycle; D, day (e.g. C1D1, cycle 1, day 1). Note: Data represent median plasma concentration (lowest to highest) in patients who started with sunitinib 50 mg in each treatment cycle.

on Schedule 4/2, was effective and well-tolerated for the first- and second-line treatment of metastatic RCC in Japanese patients. This is the first such study of this magnitude of patients in Japan.

Data revealed similar ORRs in the two patient populations, 48.0% and 46.0% in the first-line and pretreated patients, respectively, with identical findings reported by investigator and independent reviewers. Although cross-study comparisons should be interpreted with care owing to differences in methodology, these results compare favourably with those from previous, larger trials of sunitinib in treatment-naïve (47%) (17) and cytokine-refractory patients (33%) (14–16) with metastatic RCC, as well as with the ORR of 12.4% recently reported for sorafenib in a phase II study of Japanese patients with cytokine-refractory metastatic RCC (24). In addition, as reported in previous trials (14–17), sunitinib was associated with substantially longer PFS in the first-line population compared with the pretreated population (46.0 vs. 33.6 weeks, respectively).

All patients experienced treatment-related adverse events, the majority of which were grade 1 or 2 in severity. Most patients were able to resume therapy following treatment changes, with only five patients (20%) in the first-line population and four patients (15%) in the pretreated population having discontinued because of adverse events. The most commonly reported grade 3 adverse events and laboratory abnormalities were diarrhoea, hand-foot syndrome and decreased platelets in the first-line population, and fatigue and decreased neutrophils and platelets in the pretreated population. In particular, the incidence of grade 3/4 haematological toxicities such as decrease of neutrophils and platelets seems to be higher in this trial when compared with the previous worldwide data, more than 50% versus around 10%, respectively.

There were modest declines in health-related quality of life during the sunitinib treatment periods as measured by EQ-5D and EQ-VAS, which readily recovered during the subsequent off-treatment periods. In addition, overall scores were slightly lower at the end of treatment compared with baseline, and the data suggested a slight, non-significant trend towards higher scores in the pretreated over the first-line population.

Preclinical studies have demonstrated that sunitinib is effective at plasma concentrations $\geq$50 ng/ml (23). In the current study, therapeutically effective levels of the drug were reached after 2 weeks of treatment during cycle 1, levels which, although cyclic, reflecting the dosing schedule, were sustained for the duration of treatment in both populations. Repeated dosing was not associated with accumulation of sunitinib in plasma.

Houk et al. (25) analysed merged data from 13 Western studies (including Japanese subjects in one study) and one Japanese study using a population-PK approach, and demonstrated that tumour type (i.e. metastatic RCC, gastrointestinal stromal tumours or other solid tumours) as a covariate contributed the largest effect on the PK of sunitinib and SU12662. Gender, body weight and ECOG PS score had less of an impact, and Japanese patients showed similar PK to Caucasians. They concluded that no starting sunitinib dose adjustments are recommended based on the magnitude of predicted changes owing to any covariate studied. Correlations between body weight and AUC values of sunitinib, SU12662 and total drug in Japanese and Caucasian subjects from the above 13 Western studies and one Japanese study were further investigated, and no clear correlations

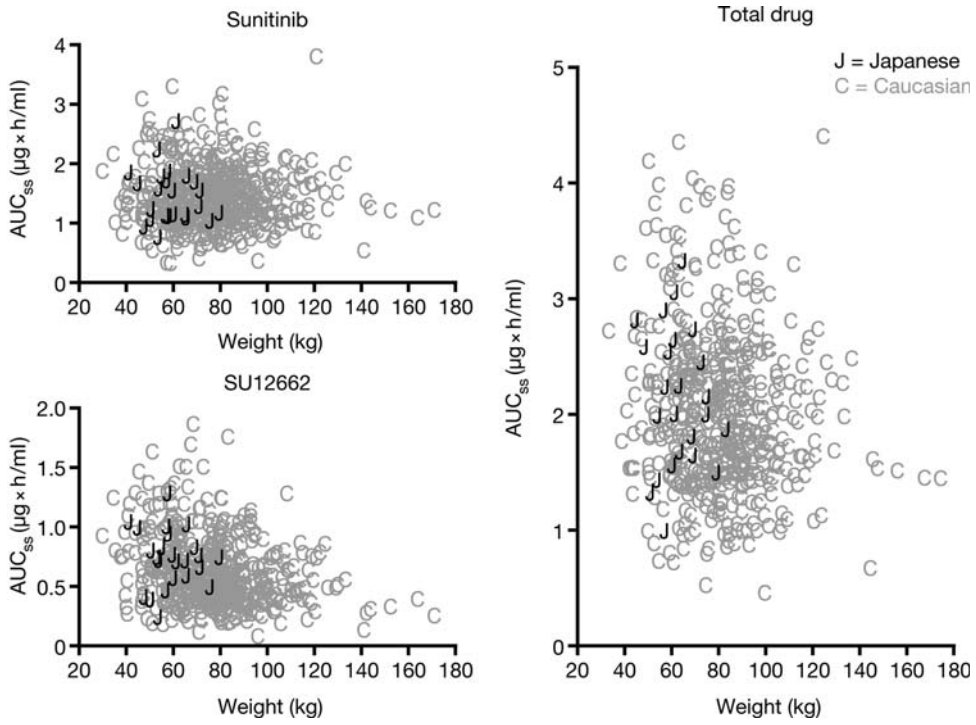

Figure 4. Correlations between the steady state AUC values (sunitinib, SU12662 and total drug) and the body weight of individual Caucasian (C) and Japanese (J) subjects from 13 Western studies (including Japanese subjects in one study) and one Japanese study described in reference (25).

between the AUC values and body weight were identified in either population (Figure 4). Importantly, although the body weights of Japanese subjects were generally lower when compared with those of Caucasian subjects, the AUC values seen in Japanese subjects were within the range of those seen in Caucasian subjects, indicating no substantial difference in the AUC of sunitinib, SU12662 or total drug between these two populations.

The incidence of haematological adverse events was numerically higher in this trial with Japanese patients ($n = 51$) compared with those previously reported for sunitinib in Western patients ($n = 375$) (17). Better understanding of the mechanisms underlying the side effects of sunitinib is of great interest and may help explain this difference. Since the AUC values of sunitinib and SU12662 were similar between Japanese and Caucasian subjects (Figure 4), the likely disparities in the adverse event profiles may be explained by differences in the relative importance (e.g. expression levels and activity) of sunitinib-sensitive kinases that are involved in the homeostatic regulation of the haematopoietic system. However, given the small number of Japanese patients in this trial ($n = 51$), it is still to be statistically determined whether substantial racial/ethnic differences exist in the pharmacological properties of sunitinib.

CONCLUSION

Sunitinib 50 mg administered on Schedule 4/2 is effective and well-tolerated for the treatment of Japanese patients with metastatic RCC in both the first- and second-line treatment settings. It is also of note that there was a trend towards a greater antitumour efficacy and higher incidence of haematological adverse events in Japanese patients compared with the mostly Western patients who participated in prior trials, warranting further investigation.

AUTHORSHIP CONTRIBUTIONS

All authors discussed the results and commented on the manuscript. Specifically, each author contributed to the study and manuscript as follows: Hirotsugu Uemura designed this study, conducted patient treatment and wrote/edited the manuscript; Nobuo Shinohara, Takeshi Yuasa, Yoshihiko Tomita, Hiroyuki Fujimoto, Soichi Mugiya, Masashi Niwakawa designed this study, conducted patient treatment and edited the manuscript; Tsuneharu Miki designed this study and edited the manuscript; Norio Nonomura, Masayuki Takahashi, Yoshihiro Hasegawa designed this study, conducted patient treatment and edited the manuscript; Naoki Agata analysed the data and wrote/edited the manuscript; Brett Houk analysed the data and edited the manuscript; Seiji Naito designed this study, conducted patient treatment and edited the manuscript; and Hideyuki Akaza designed this study, conducted patient treatment, edited the manuscript and serves as the corresponding author for this paper.

Acknowledgements

We would like to thank all the patients and their families and caregivers for their participation in this study and investigators and their staff from participating sites.

Funding

This work was supported by funding from Pfizer Inc. Editorial assistance was provided by ACUMED® (Tytherington, UK) with funding by Pfizer Inc.

Conflict of interest statement

The authors, Naoki Agata Ph.D. and Brett Houk Ph.D., are employees of Pfizer Inc.

References

1. Kosary CL, McLaughlin JK. Kidney and renal pelvis. In: Miller BA, Ries LAG, Hankey BF, et al. editors. *SEER Cancer Statistics Review, 1973–1990*. Bethesda, MD: National Cancer Institute, 1993; (NIH publication no. 93–2789, XI.1–XI.22).
2. Belldegrum A, deKernion JB. Renal tumours. In: Walsh PC, Retik AB, Vaughan ED, Jr, Wein AJ editors. *Campbell's Urology*. 7th edn. Philadelphia, PA: WB Saunders Company, 1998;2283–326. p.
3. Vogelzang NJ, Stadler WM. Kidney cancer. *Lancet* 1998;352:1691–6.
4. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of eighteen major cancers in 1985. *Int J Cancer* 1993;54:594–606.
5. Marumo K, Kanayama H, Miyao N, Nakazawa H, Ozono S, Horie S, et al. The Japanese Study Group Against Renal Cancer. Prevalence of renal cell carcinoma: a nation-wide survey in Japan, 2002. *Int J Urol* 2007;14:479–82.
6. Lam JS, Leppert JT, Belldegrun AS, Figlin RA. Novel approaches in the therapy of metastatic renal cell carcinoma. *World J Urol* 2005;23:202–12.
7. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. *N Engl J Med* 1996;335:865–75.
8. Janzen NK, Kim HL, Figlin RA, Belldegrun AS. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. *Urol Clin North Am* 2003;30:843–52.
9. Négrier S, Escudier B, Lasset C, Douillard JY, Savary J, Chevreau C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Francais d'Immunotherapie. *N Engl J Med* 1998;338:1272–8.
10. Schöffski P, Dumez H, Clement P, Hoeben A, Prenen H, Wolter P, et al. Emerging role of tyrosine kinase inhibitors in the treatment of advanced renal cell cancer. A review. *Ann Oncol* 2006;17:1185–96.
11. Escudier B. Advanced renal cell carcinoma: current and emerging management strategies. *Drugs* 2007;67:1257–64.
12. Hutson TE, Figlin RA. Evolving role of novel targeted agents in renal cell carcinoma. *Oncology (Williston Park)* 2007;21:1175–80. discussion 1184, 1187, 1190.
13. Chow LQ, Eckhardt SG. Sunitinib: from rational design to clinical efficacy. *J Clin Oncol* 2007;25:884–96.
14. Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Wilding G, Figlin RA, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006;24:16–24.
15. Motzer RJ, Rini BI, Bukowski RM, Curti BD, George DJ, Hudes GR, et al. Sunitinib in patients with metastatic renal cell carcinoma. *JAMA* 2006;295:2516–24.
16. Motzer RJ, Michaelson MD, Rosenberg J, Bukowski RM, Curti BD, George DJ, et al. Sunitinib efficacy against advanced renal cell carcinoma. *J Urol* 2007;178:1883–7. Published online 17 September 2007.
17. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:3584–90.
18. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumours. *J Natl Cancer Inst* 2000;92:205–16.
19. Brazier J, Jones N, Kind P. Testing the validity of the EuroQol and comparing it with the SF-36 health survey questionnaire. *Qual Life Res* 1993;2:169–80.
20. de Boer AG, van Lanschot JJ, Stalmeier PF, van Sandick JW, Hulscher JB, de Haes JC, Sprangers MA. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? *Qual Life Res* 2004;13:311–20.
21. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33:337–43.
22. Kaplan E, Meier P. Nonparametric estimation for incomplete observations. *J Am Stat Assoc* 1958;53:457–81.
23. Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, et al. *In vivo* antitumour activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res* 2003;9:327–37.
24. Akaza H, Tsukamoto T, Murai M, Nakajima K, Naito S. Phase II study to investigate the efficacy, safety, and pharmacokinetics of sorafenib in Japanese patients with advanced renal cell carcinoma. *Jpn J Clin Oncol* 2007;37:755–62.
25. Houk BE, Bello CL, Kang D, Amantea M. A population pharmacokinetic meta-analysis of sunitinib malate (SU11248) and its primary metabolite (SU12662) in healthy volunteers and oncology patients. *Clin Cancer Res* 2009;15:2497–506.