Overview

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Title: Phase I Study of Sunitinib in Combination With Gemcitabine and Capecitabine for First-Line Treatment of Metastatic or Unresectable Renal Cell Carcinoma

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Author Summary: Abstract and Brief Discussion

Background

The combination of gemcitabine plus capecitabine and sunitinib (GCS) shows activity in metastatic renal cell carcinoma (mRCC). We tested the multitargeted "chemo-switch" regimen as first-line treatment in patients with mRCC.

Methods

We assessed the maximum tolerated dose and antitumor activity of GCS in treatment-naïve, advanced mRCC patients. Treatment consisted of intravenous gemcitabine on days 1 and 8, oral capecitabine twice daily on days 1–14, and oral sunitinib daily for six 21-day cycles, followed by sunitinib monotherapy at the investigator's discretion. Dose level 0 (DL0) was gemcitabine 1,000 mg/m^2 per day plus capecitabine 650 mg/m^2 per 12 hours plus sunitinib 37.5 mg/day; DL1 was gemcitabine 1,000 mg/m^2 per day plus capecitabine 850 mg/m^2 per 12 hours plus sunitinib 37.5 mg/day.

Results

Sixteen patients were enrolled. At DL1, two of four patients had dose-limiting toxicity (DLT; grade 3 diarrhea and grade 4 thrombocytopenia). The dose was reduced to DL0 when only 1 of 12 patients experienced DLT (grade 3 diarrhea, grade 3 mucositis, and grade 3 thrombocytopenia). Dose reductions were frequent (58% of patients), and only seven patients were able to receive the three drugs for more than three cycles. One patient achieved a complete response, three had partial responses, and the best response for four was stable disease.

Conclusion

The safety profile of the combination does not seem manageable in this patient population. No further development of the combination is recommended.

Discussion

Treatment with agents targeting vascular endothelial growth factor (VEGF) receptors and mammalian target of rapamycin have reached a plateau in terms of median progression-free and overall survival, and several strategies have attempted to improve the outcome.

Pietras et al. developed the "chemo-switch" concept, applying the combination of targeted agents with chemotherapy using the standard maximum tolerated doses (MTDs) in combination with low doses of chemotherapeutic drugs given continuously on a daily basis (metronomic chemotherapy). A synergistic effect has been demonstrated in xenograft mouse models, and we saw promising data in a prior clinical trial.

The tyrosine kinase inhibitor sunitinib inhibits several receptor tyrosine kinases, including VEGF and platelet-derived growth factor 2 (PDGF2), and has shown efficacy in patients with metastatic renal cell carcinoma (mRCC), as first- and as second-line treatment [3, 4]. It is believed that the anti-VEGF and the anti-PDFG effects act in a synergistic way with metronomic chemotherapy. Consequently, the triple combination of gemcitabine plus capecitabine and sunitinib was tested in our phase I study as first-line therapy in advanced RCC or mRCC patients to determine the MTD, to assess safety, and to observe preliminary efficacy results [5].

Three patients showed dose-limiting toxicity (DLT), two at dose level 1 (DL1; grade 4 thrombocytopenia in one patient and grade 3 diarrhea and thrombocytopenia in the other) and one at DL0 (grade 3 mucositis and thrombocytopenia). One grade 5 cardiovascular toxicity unrelated to trial medication was seen. Eight patients suffered serious adverse events (SAEs). The study treatment-related causes for hospitalization in the other SAE-presenting patients were thrombocytopenia, neutropenia, mucositis, hypertensive crisis, asthenia, and anorexia. In addition, other AEs not related to the study medication caused hospitalization or prolonged hospitalization. Disease progression was reported as the cause of hospitalization in three patients, and it was not considered related to the study medication in any case.

The regimen was poorly tolerated by patients, and more than half experienced asthenia, neutropenia, thrombocytopenia, mucositis, diarrhea, or nausea. The combination of gemcitabine plus capecitabine alone in RCC patients showed a high incidence of grade 3–4 neutropenia and persistent grade 1–2 fatigue and gastrointestinal toxicities in addition to hand-foot syndrome events that would generally be unacceptable by a large percentage of patients [6]. Although hand-foot syndrome is also a common adverse event of sunitinib [7, 8], the incidence of this event in our study was low (four events in three patients) compared with that observed in the study using gemcitabine plus capecitabine alone [6], probably due to the lower dose of capecitabine in the current study.

Although data on efficacy are limited, the triple combination does not seem to be better than sunitinib alone as first-line treatment [4, 8] and as second-line treatment [3, 9].

The use of sunitinib in combination with gemcitabine at MTDs followed by capecitabine administered in a metronomic way, exploring the chemo-switch concept, did not prove feasible because of toxicity and premature treatment discontinuation. This triple combination cannot be recommended for further study.

Trial Information

Disease	Renal cell carcinoma – clear cell
Disease	Renal cell carcinoma – not clear cell
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	No designated number of regimens
Type of study - 1	Phase I
Type of study - 2	Other
Primary Endpoint	Maximum Tolerated Dose
Secondary Endpoint	Tolerability
Additional Details of Endpoints or Study Design	
Investigator's Analysis	Poorly Tolerated/Not Feasible

Drug Information

Drug 1 **Generic/Working name**	Sunitinib
Trade name	SUTENT
Company name	Pfizer
Drug class	Angiogenesis - VEGF
Dose	50 mg/day
Schedule of Administration	Daily for six 21-day cycles, followed by sunitinib monotherapy
Drug 2 **Generic/Working name**	Gemcitabine
Drug class	Other
Dose	1,000 mg/m^2 per day
Schedule of Administration	On days 1 and 8
Drug 3 **Generic/Working name**	Capecitabine
Drug class	Other
Dose	1,000 mg/m^2 b.i.d.
Schedule of Administration	Twice daily on days 1–14

Dose Level	Dose of Drug: Sunitinib	Dose of Drug: Gemcitabine	Dose of Drug: Capecitabine	Number Enrolled	Number Evaluable for Toxicity
DL0	37.5 mg/day	1,000 mg/m^2 per day	650 mg/m^2 b.i.d.	12	12
DL1	37.5 mg/day	1,000 mg/m^2 per day	850 mg/m^2 b.i.d.	4	4

Patient Characteristics

Number of patients, male	13
Number of patients, female	3
Stage	
	II
	III
	IV
	Metastatic
Age	Median (range): 66.5 (43–78)
Number of prior systemic therapies	Median (range): Not Collected
Performance Status:	ECOG
	0—7
	1—8
	2—
	3—
	Unknown—
Cancer Types or Histologic Subtypes	Clear cell 11
	Papillary carcinoma 4
	Other: Clear cell plus sarcomatoid component 1

Primary Assessment Method

Experimental Arm: Total Patient Population

Number of patients enrolled	16
Number of patients evaluable for toxicity	16
Evaluation method	Other

Dose limiting toxicity

Dose Level	Dose of Drug: Sunitinib	Dose of Drug: Gemcitabine	Dose of Drug: Capecitabine	Number Enrolled	Number Evaluable for Toxicity	Number With a Dose Limiting Toxicity	Dose Limiting Toxicity Information
DL0	37.5 mg/ day	1,000 mg/m^2 per day	650 mg/m^2 b.i.d.	12	12	1	Neutropenia, thrombocytopenia, hypovolemic shock, neutropenia, thrombocytopenia, diarrhea, mucositis
DL1	37.5 mg/ day	1,000 mg/m^2 per day	850 mg/m^2 b.i.d.	4	4	2	2× thrombocytopenia, hyperglucemia, diarrhea, low GI hemorrhage, mucositis

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics / Pharmacodynamics	Not Collected
Investigator's Assessment	Poorly Tolerated/Not Feasible

Discussion

Treatment with agents targeting vascular endothelial growth factor (VEGF) receptors and mammalian target of rapamycin have reached a plateau in terms of median progression-free survival (PFS) and overall survival (OS), and several strategies have attempted to improve the outcomes of patients receiving these therapies. Pietras et al. introduced the "chemo-switch" concept, which combines targeted agents with chemotherapy using standard maximum tolerated doses (MTDs) in combination with low doses of chemotherapeutic drugs given continuously on a daily basis (metronomic chemotherapy). Using this approach, a synergistic effect has been demonstrated in a mouse model.

The tyrosine kinase inhibitor sunitinib inhibits several receptor tyrosine kinases, including VEGF and platelet-derived growth factor 2 (PDGF2), and has shown efficacy in patients with metastatic renal cell carcinoma (mRCC), as first- and second-line treatment [3, 4]. It is believed that the anti-VEGF and anti-PDFG effects act in a synergistic way with metronomic chemotherapy. Consequently, the triple combination of gemcitabine plus capecitabine and sunitinib was tested in our phase I study in advanced RCC and mRCC patients to determine the MTD, to assess safety, and to observe preliminary efficacy results [5].

An open-label phase I dose-escalation study was conducted to determine the MTD and the safety profile of sunitinib in combination with gemcitabine and capecitabine (GC) in sunitinib-naive patients with advanced RCC or mRCC and assessed treatment efficacy in terms of objective response (complete response [CR] or partial response [PR]) and disease control rate (CR, PR, or stable disease [SD]) and to find out the OS and PFS of treated patients (Table 1).

A 3＋3 dose escalation rule was followed with three patients initially enrolled at dose level 0 (DL0). The MTD is the DL at which two of three or two of six patients exhibit DLT during the first treatment cycle. The DL at which one or more of six patients exhibits DLT is the recommended dose for phase II studies.

Three patients were enrolled at DL0 and showed no DLT at the first cycle. Thus, two patients were enrolled at DL1. Neither patient showed DLT; however, the following two did present DLT (grade 4 thrombocytopenia in one patient and grade 3 diarrhea, mucositis, and thrombocytopenia in the other). The toxicity profile observed in the four patients included in DL1, with significant hematologic toxicities from the second cycle on, resulted in the decision not to include any more patients at DL1. Three more patients were enrolled at DL0, and none exhibited DLT; then, six additional patients were enrolled for confirmation of DL0 as the MTD. Only 1 of the 12 patients experienced DLT (grade 3 mucositis and thrombocytopenia); therefore, the MTD was sunitinib 37.5 mg, capecitabine 650 mg/m^2, and gemcitabine 1,000 mg/m^2.

All 16 patients were evaluated for safety, and all showed at least one adverse event related to the study drugs, most grade 1 or 2. As per investigator assessment, 49% of drug-related events were related to the combination of the three drugs; 29% were related to chemotherapy (either gemcitabine or capecitabine or GC), 3.6% to sunitinib and capecitabine, and 18% to sunitinib alone. Eight patients suffered serious adverse events (SAEs) (Tables 2–4).

Three patients showed DLT, two at DL1 (grade 4 thrombocytopenia in one patient and grade 3 diarrhea, mucositis, and thrombocytopenia in the other) and one at DL0 (grade 3 mucositis and thrombocytopenia). Eight patients suffered SAEs. Hypovolemic shock, which caused the death of one patient, was not considered related to any study drug but most likely to a cardiovascular event, based on prior patient medical history. The study treatment-related causes for hospitalization in the other SAE-presenting patients were thrombocytopenia, neutropenia, mucositis, hypertensive crisis, asthenia, and anorexia.

The regimen was poorly tolerated, and more than half of the patients showed asthenia, neutropenia, thrombocytopenia, mucositis, diarrhea, and nausea. The combination of GC alone in RCC patients resulted in a high incidence of grade 3–4 neutropenia, persistent grade 1–2 fatigue, gastrointestinal toxicities, and hand-foot syndrome—events generally unacceptable to a large percentage of patients [6]. Although hand-foot syndrome is also a common adverse event of sunitinib [7, 8], its incidence in our study was low (four events in three patients) compared with that observed in the study using GC alone [6], probably due to the lower dose of capecitabine in the current study.

All patients ($n = 16$) were assessed for progression-free and overall survival. Median PFS was 7.8 months (95% confidence interval [CI]: 2.5 to not reported), and median OS was 8.1 months (95% CI: 6.5–9.7).

Twelve patients were assessable for treatment response according to Response Evaluation Criteria In Solid Tumors. At DL0, four patients (33%) achieved an objective response (one CR and three PRs) and five achieved SD. Both assessable patients at DL1 also achieved SD. Thus, 8 of 12 assessable patients had overall clinical benefit (1 CR, 3 PR, and 7 SD), and the overall disease control rate was 91.7%.

Although data on efficacy were limited, the triple combination does not seem to offer a better alternative than sunitinib alone as first-line treatment [4, 8] or second-line treatment[3, 9].The use of sunitinib in combination with gemcitabine at MTDs followed by capecitabine administered in a metronomic way, exploring the chemo-switch concept, proved not to be feasible because of toxicity and premature treatment discontinuation. This triple combination cannot be recommended for further study.

Acknowledgment

J.B. is currently affiliated with Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA.

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Figures and Tables

Table 1. Patient characteristics

Characteristics	Results
Race: White, *n* (%)	16 (100)
Sex: Male, *n* (%)	13 (81.3)
Age, years, median (range)	66.5 (43–78)
BMI, kg/m2, median (range)	25.5 (20.6–33.5)
ECOG, *n* (%)[a]	
1	8 (53.3)
0	7 (46.7)
Time since diagnosis, months, median (range)	15 (0.1–81.1)
Primary tumor characteristics, *n* (%)	
Histology	
Clear cells	11 (68.8)
Papillary carcinoma	4 (25.0)
Other: clear cells plus sarcomatoid component	1 (6.3)
TNM stage, *n* (%)	
II	1 (6.7)
III	1 (6.7)
IV	13 (86.7)
Motzer risk, *n* (%)	
Favorable (0)	7 (43.8)
Intermediate (1–2)	7 (43.8)
Poor (≥3)	2 (12.5)
Metastasis, *n* (%)	
Liver	3 (18.8)
Bone	3 (18.8)
Lung	9 (56.3)
Other[b]	11 (68.8)
Number of locations with metastases, *n* (%)	
1	7 (43.8)
2	3 (18.8)
≥3	6 (37.5)

[a]Data not available for one patient.
[b]Retroperitoneal (2), adrenal (2), testicular (1), adenopathy (2), ovary (1), kidney (1), muscle (1), soft tissue (1). Numbers in parentheses equal to number of patients.
Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.

Table 2. Patients' best response and grade 3–4 adverse events

Patient	DL	No. of cycles	Study exit	DLT	Best response	Grade 3–4 AEs
301	0	4	AE	No	SD	2× Neutropenia, asthenia
102	0	6	End	No	CR	RLC, 3× neutropenia, DVT
303	0	5	AE	No	—	2× Neutropenia, 2× thrombocytopenia
204	1	6	End	No	SD	Leukopenia, neutropenia, thrombocytopenia, hypertension
305	1	3	AE	No	SD	Neutropenia, thrombocytopenia, 3× asthenia
106	1	1	Death	**Yes**	—	Neutropenia, thrombocytopenia, hypovolemic shock
107	1	1	AE	**Yes**	—	Neutropenia, thrombocytopenia, diarrhea, mucositis
208	0	2	Progression	No	PR	UTI
209	0	6	End	No	PR	
110	0	3	AE	No	SD	Trombocytopenia Anorexia, diarrhea, 3× asthenia
111	0	3	AE	**Yes**	—	2× Thrombocytopenia, hyperglucemia, diarrhea, low GI hemorrhage, mucositis
212	0	6	End	No	SD	Thrombocytopenia
213	0	2	AE	No	PR	Neutropenia, mucositis
114	0	4	Progression	No	SD	Anemia, neutropenia, artralgia
315	0	4	Progression	No	SD	
216	0	2	Progression	No	PD	Neutropenia

Abbreviations: —, nonassessable for efficacy; ; ×, times; AE, adverse event; CR, complete response; DLT, dose limiting toxicity; DVT, deep venous thrombosis; GI, gastrointestinal; PD, progressive disease; PR, partial response; RLC, leukopenia count; SD, stable disease; UTI, urinary tract infection.

Table 3. Patients with severe adverse events

Patient history	Hospital admission 1	Hospital admission 2	Hospital admission 3	Hospital admission 4
Aged 75 years, male; hypertension, hyperuricemia, nephrectomy; concomitant medication: ramipril, atenolol, allopurinol	G4 thrombocytopenia (treatment discontinued)	Hypovolemic shock due to CV cause secondary to dehydratation; oliguria, hypotension without fever and unknown blood counts—death not related to study treatment		
Aged 76 years, male	G3 thrombocytopenia, mucositis, and diarrhea (all related to the three drugs; treatment permanently discontinued)			
Aged 67 years, male; controlled hypertension, atrial flutter, and inguinal pain	Inguinal pain, respiratory infection and lower limb edema (none related to study medication)	G3 diarrhea and G2 mucositis, (both S and C related); G3 asthenia (related to the three drugs)	G4 thrombocytopenia, (related to the three drugs; treatment permanently discontinued); G2 nausea and diarrhea; G3 asthenia and anorexia	Deteriorated general condition; released 6 days later; hospitalized again due to disease progression, died 1 day later

Aged 78 years, male	G2–3 mucositis (S and C related); G3 thrombocytopenia (related to the 3 drugs; C and G were reduced)	Diabetic debut (not related to treatment)	G3 diarrhea (S and C-related); abdominal pain (C-related); GI hemorrhage
Aged 58 years, male; withdrew from the study	Disease progression, died 12 days later		
Aged 78 years, male	S-related hypertensive crisis (solved on the same day); G4 thrombocytopenia (related to the 3 drugs) requiring platelet transfusion		
Aged 53 years, male	Non-neutropenic fever due to Enterobacter urinary infection (not related to study treatment); epileptic crisis prolonged the hospitalization; disease progression		
Aged 43 years; patient on heparin treatment; intermittent hematuria, heparin treatment was interrupted	Hematuria recurred (first reported as S-related SUSAR but later considered related to heparin medication)		

Abbreviations: C, capecitabine; G, gemcitabine; G2, grade 2; G3, grade 3; G4, grade 4; GI, gastrointestinal; S, sunitinib; SUSAR, suspected unexpected serious adverse reaction.

Table 4. Drug-related adverse events

			Grade			Drug related				
AEs	**Patients, *n* (%)**	**No. of AEs**	**1 + 2**	**3 + 4**	**Uk**	**S**	**SC**	**C/G**	**Tt**	**Uk**
Complementary tests		3								
Increased γ-glutamyltransferase	1 (6.3)	1	1						1	
Decreased hemoglobin	1 (6.3)	1	1						1	
Decreased leukocyte count	1 (6.3)	1		1					1	
Infections and infestations		1								
Nasopharyngitis	1 (12.5)	1	1						1	
Surgical and medical procedures		1								
Nasal blockage	1 (6.3)	1	1						1	
Skin and subcutaneous tissue disorders		13								
Alopecia	1 (6.3)	1	1			1				
Rush	2 (12.5)	2	2				1		1	

Pruritus	1 (6.3)	1	1					1		
Palmar-plantar erythrodysthesia syndrome	3 (18.8)	4	4			1	2	1		
Skin disorders	1 (6.3)	1	1			1				
Pigmentation disorders	1 (6.3)	1	1			1				
Blood and lymphatic system disorders		59								
Anemia	2 (12.5)	2	1	1					2	
Leukopenia	5 (31.3)	6	5	1				4	2	
Neutropenia	12 (75)	25	11	14		1		15	8	1
Thrombocytopenia	9 (56.3)	26	16	10		8	2	7	9	
Metabolism and nutrition disorders		11								
Anorexia	6 (37.5)	11	10	1					9	2
Nervous system disorders		3								
Dysesthesia	2 (12.5)	2	2						2	
Somnolence	1 (6.3)	1	1						1	
Endocrine disorders		2								
Hypothyroidism	2 (12.5)	2	1		1	2				
Gastrointestinal disorders		65								
Dry mouth	4 (25)	5	5						5	
Diarrhea	11 (68.8)	21	18	3		7	1	9	4	
Dysgeusia	4 (25)	5	5			1		1	3	
Heartburn/dyspepsia	3 (18.8)	4	4					3	1	
Abdominal pain	1 (6.3)	1	1				1			
Dental pain	1 (6.3)	1	1						1	
Pain in the upper abdomen	2 (12.5)	4	4					1	3	
Constipation	1 (6.3)	1	1						1	
Flatulence	1 (6.3)	1	1						1	
Gingivitis	2 (12.5)	2	2					1	1	
Glositis	1 (6.3)	1	1					1		
Low GI tract hemorrhage	1 (6.3)	1		1				1		
Dental pain	1 (6.3)	1	1					1		
Nausea	9 (56.3)	14	14			1		6	7	
Vomiting	3 (18.8)	3	2		1			1	2	
General disorders and administration site conditions		76								
Asthenia	13 (81.3)	46	38	8		11		6	29	
Peripheral edema	2 (12.5)	2	2			2				
Mucositis	11 (68.8)	23	19	3	1		2	9	12	
Pirexia	3 (18.8)	4	4					2	2	
Dry mucus	1 (6.3)	1	1						1	
Musculoskeletal and soft tissue disorders		1								
Joint pain	1 (6.3)	1	1						1	
Eye disorders		3								
Conjunctivitis	1 (6.3)	1	1			1				
Increased tear production	1 (6.3)	1	1					1		
Dry eye	1 (6.3)	1	1			1				

Psychiatric disorders		1								
Insomnia	1 (6.3)	1	1						1	
Renal and urinary disorders		1								
Dysuria	1 (6.3)	1	1			1				
Respiratory, thoracic, and mediastinal disorders		9								
Dysphonia	1 (6.3)	2	2						2	
Epistaxis	4 (25)	5	5					2	3	
Hiccups	1 (6.3)	1	1						1	
Nasal ulcer	1 (6.3)	1	1						1	
Vascular disorders		6								
Hypertension	5 (31.3)	6	5	1		6				
Total events		252	205	44	3	46	9	73	121	3

Abbreviations: AEs, adverse events; G/C, gemcitabine and/or capecitabine; GI, gastrointestinal; S,sunitinib; SC, sunitinib and capecitabine; Tt, three-drug combination treatment; Uk, unknown.