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Sunitinib malate for metastatic castration-resistant prostate cancer following docetaxel-based chemotherapy

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Background: Systemic therapy options are limited for metastatic castration-resistant prostate cancer (CRPC) patients who progress following docetaxel (Taxotere). This phase II trial evaluated sunitinib malate in patients with progressing metastatic CRPC following prior docetaxel.

Patients and methods: Patients with metastatic CRPC progressing following one to two chemotherapy regimens including docetaxel were included. The primary end point was progression-free survival (PFS) per radiographic and clinical evaluations. Oral sunitinib was administered 50 mg/day 4-weeks on followed by 2-weeks off per cycle up to a maximum of eight cycles or until clinical progression or intolerable toxicity.

Results: Thirty-six patients with a median age of 69.5 years were accrued. The median PFS was 19.4 weeks with a 12-week PFS of 75.8%. Four patients (12.1%) had a ≥50% prostate-specific antigen (PSA) decline and seven (21.2%) had a ≥30% PSA decline. Two of 18 patients (11.1%) with measurable disease demonstrated 30% declines by RECIST and eight (44.4%) displayed some shrinkage. A decline in pain score ≥2 points occurred in 13.6% of 22 assessable patients. Drug discontinuation due to toxic effects occurred in 52.8% of patients.

Conclusion: Sunitinib malate demonstrated promising activity in metastatic CRPC progressing after prior docetaxel.

Key words: castration-resistant prostate cancer, sunitinib malate

introduction

Docetaxel-based chemotherapy has a palliative role in patients with metastatic castration-resistant prostate cancer (CRPC) with a median overall survival (OS) of 19 months and a median progression-free survival (PFS) of 6 months [1–3]. Following docetaxel, effective salvage options are lacking [4, 5]. Sunitinib malate is an orally administered multitargeted tyrosine kinase inhibitor (TKI) that is approved for metastatic renal cell cancer and gastrointestinal stromal tumors and displays selectivity for platelet-derived growth factor (PDGF) receptors, vascular endothelial growth factor (VEGF) receptors, Flt3, and Kit [6–8]. Given the preclinical evidence for the role of VEGF and PDGF receptor signaling in promoting prostate cancer growth, a rationale can be made to evaluate sunitinib for patients with progressive metastatic CRPC following docetaxel [9–12].

Advanced prostate cancer is characterized by a poor ability to measure response due to immeasurable bone-only metastases or prostate-specific antigen (PSA)-only disease. Although a ≥30% PSA decline in 3 months may be a useful surrogate for outcomes with chemotherapeutic agents, its validity with biological agents is unknown [13–15]. In addition, discordant PSA and clinical responses have been observed with sorafenib [16]. Other useful intermediate surrogates such as circulating tumor cells require further validation [17]. Time-to-event end points may be clinically useful surrogates and are currently recommended by the Prostate Cancer Working Group-2 guidelines [15]. In particular, PFS defined as a composite end point constituted by symptomatic or radiological progression may be a relevant end point that dictates clinical decision making and appears to be a useful intermediate surrogate for survival [18].

patients and methods

patients

Key inclusion criteria included histologically confirmed adenocarcinoma of the prostate with radiographic metastatic disease who had received one to two prior chemotherapy regimens including docetaxel (Taxotere; Sanofi-Aventis, Bridgewater, New Jersey). Progressive disease by PSA or clinical criteria was required. PSA progression was defined as a baseline increase followed by any serial increase after 2 weeks, with the last confirmatory PSA

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being ≥10 ng/ml. The Eastern Cooperative Oncology Group (ECOG) performance status was required to be zero to two. Androgen ablation therapy (luteinizing hormone-releasing hormone agonist or orchiectomy) with testosterone level <50 ng/dl was required. Adequate cardiac function by investigator judgment was required with no uncontrolled arrhythmia or hypertension, with radiological cardiac evaluation as per investigator discretion. Adequate renal, hepatic, and hematological function was also required. Patients who had received prior radionuclides or radiation to >50% of the bone marrow were excluded. Significant bleeding in the previous 4 weeks and significant acute cardiovascular morbidities in the previous 6 months were exclusion criteria. Additionally, previous radiation therapy, surgery and systemic therapy were required to be completed >4 weeks before therapy.

study design

This was an open label, phase II trial conducted at 10 community cancer centers in the US Oncology Network. Patients were treated with sunitinib until progressive disease or intolerable toxicity and for a maximum of eight 6-week cycles. The composite PFS primary end point was similar to the definition of progression employed in the large phase III Satraplatin and Prednisone against Refractory Cancer salvage trial [5]. PSA increases were not used to determine progression. Progression was defined as the first occurrence of any of the following: two distinct new lesions on bone scan, progression of measurable disease by RECIST criteria, worsening of pain by ≥2 points on the six-point present pain intensity (PPI) scale, urinary tract obstruction, bone-related events (pathological fracture, spinal cord compression, need for palliative radiation, surgery or kyphoplasty to any neoplastic bone lesion) or a deterioration of performance status to an ECOG score of three or four [19, 20]. The secondary end points were PSA declines (≥30% and ≥50%), PSA-doubling time (DT), measurable disease response rate by RECIST, quality of life (QoL) by Functional Assessment of Cancer Therapy-prostate (FACT-P), PPI, safety and survival [19–22]. The protocol was approved by a central Institutional Review Board.

administration of study therapy

Patients received sunitinib 50 mg/day orally on days 1–28 of each 6-week cycle for up to a maximum of eight cycles or until progression, unacceptable toxicity or withdrawal of consent. Up to two dose reductions were allowed with the dose adjusted to 37.5 mg/day and then to 25 mg/day in the event of toxic effects. For grade 3 or 4 toxic effects, the treatment was withheld until the patient recovered completely or to grade 1 toxicity, followed by resumption at a first level dose reduction. Patients who were off therapy for >3 weeks were removed from therapy.

assessments

Safety assessments were carried out every cycle (6 weeks) or earlier if clinically indicated and up to 30 days following the last dose of sunitinib. The severity of toxic effects was graded using the National Cancer Institute—Clinical Trial Criteria for Adverse Events version 3 [22]. The PSA-DT was assessed at baseline and on therapy. The PPI was self-assessed daily during treatment. After baseline radiological work-up, subsequent radiological evaluations were carried out every two cycles (12 weeks) or earlier if clinically indicated. Cardiac function evaluation was carried out according to the investigator discretion. Laboratory evaluations (complete blood cell counts and comprehensive metabolic panel), PSA, and FACT-P QoL assessments were repeated every 6 weeks. Generalized trends in use of pain medication were calculated based on reports by the patient as stable, increased, or decreased in each cycle compared with the prior 6-week cycle.

statistical methods

The median PFS with similar end points with other agents in the second-line setting after docetaxel has been ~2.5 months [4, 5]. Given the convenience of oral administration of sunitinib, modest activity was considered clinically meaningful in this relatively heavily pretreated population that had received one to two prior chemotherapy regimens. The null hypothesis for this trial was that the 12-week PFS was <15% (not clinically meaningful) with the alternative hypothesis being that the true PFS was 30%. Thirty-four patients were deemed to be required according to the STPlan (M.D. Anderson Cancer Center) with α level of 5% and 80% power. Kaplan–Meier techniques in SAS® were employed on the intention-to-treat population to assess time-to-event analyses such as PFS and OS [23]. If no major toxic effects (six or more patients with grade 4 hematological and/or grade 3 or higher non-hematological toxic effects) related to sunitinib occurred among the first 20 patients during cycle 1, the study would keep accruing. The PSA-DT was calculated by linear regression.

results

patient characteristics

Thirty-six patients with metastatic CRPC were enrolled in the trial (Table 1). The median age was 69.5 years and the median PSA was 215 ng/ml. All patients had received prior docetaxel chemotherapy, four patients (11.1%) had received prior

Table 1. Patient characteristics at baseline

Characteristic	$N = 36$
Age (years)	
Median	69.5
Range	52.6–86.5
Race, *n* (%)	
White	32 (88.9)
Black	3 (8.3)
Hispanic	1 (2.8)
ECOG performance status, *n* (%)	
0	12 (33.3)
1	21 (58.3)
2	3 (8.3)
Prior therapy, *n* (%)	
Chemotherapy[a]	36 (100)
Docetaxel	36 (100)
Mitoxantrone	2 (5.6)
Other[b]	11 (30.6)
Bevacizumab	4 (11.1)
Radiotherapy[c]	21 (58.3)
Surgery	26 (72.2)
Prostatectomy	17 (65.4)
Site of metastasis, *n* (%)	
Bone	32 (88.9)
Soft tissue/lymph node	8 (22.2)
Visceral	6 (16.7)
PSA, *n* (%)	
Median	215
Range	4.1–4033.0

[a]Subjects may have had one to two prior agents.
[b]Other included carboplatin ($n = 3$), cyclophosphamide ($n = 3$), paclitaxel ($n = 3$), estramustine ($n = 1$), and gemcitabine ($n = 1$).
[c]Sites of radiation included bone ($n = 16$), prostate ($n = 9$), pelvic ($n = 4$), and breast ($n = 1$).
ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

bevacizumab, two (5.6%) had received mitoxantrone, and 11 (30.6%) had received other agents (Table 1). The most common site of metastatic disease was bone (88.9%).

activity of sunitinib

The median PFS was 19.4 weeks with a PFS at 12 weeks of 75.8%, and a PFS of 6.2% at 48 weeks. The median survival was 43.7 weeks (range 2.6–72.7 weeks). Four patients (12.1%) had a ≥50% PSA decline and seven (21.2%) had a ≥30% PSA decline compared with baseline (Figure 1A). Of the four patients previously treated with bevacizumab, one patient displayed a ≥50% PSA decline and another displayed a ≥30% PSA decline. When examining ≥30% PSA declines stratified by best response to prior chemotherapy, 5 of 18 patients with prior response or stable disease (employing conventional clinical, PSA and RECIST) responded and 1 of 14 with prior progressive disease responded, and these data were not statistically different. Overall, 10 patients (30.3%) exhibited some decline of PSA compared with baseline, while 15 patients (45.5%) exhibited some decline of PSA compared with the previous PSA value (Table 2). The median PSA-DT was prolonged on therapy (3.1 months) compared with pretherapy (1.4 months). Two of 18 patients (11.1%) with measurable disease at baseline demonstrated unconfirmed ≥30% declines in size by RECIST and eight patients (44.4%) displayed some reduction in size compared with baseline (Figure 1B). Of the two patients with 30% RECIST declines in size, one patient experienced a ≥50% PSA decline and pain score decline ≥2 points, while the other patient had a <30% PSA decline. Declines in size could not be confirmed with another scan probably due to frequent discontinuation of therapy for toxic effects. Overall, a decline in pain score of ≥2 points was noted in three patients (13.6%), while a decline ≥1 point was noted in 11.0 (50%) of 22 assessable patients. Five of the 11 patients with declines in pain scores demonstrated discordant PSA increases. Analgesic intake decreased in six patients (17.1%) and was stable in 10 patients (28.6%). The median number of cycles completed was 2 (range 1–7); 14 patients completed one cycle of therapy, nine completed two cycles, and six completed three cycles. The primary cause of drug discontinuation was toxic effects (52.8%) followed by progressive disease (33.3%). Dose reduction to 37.5 and 25 mg daily was required in seven and three patients (8.7%), respectively. It appears that many patients preferred to discontinue therapy than continue with a dose reduction. The high proportion of drug discontinuation led to a median time-to-treatment failure (TTF) of 11.8 weeks (range 2.0–38.6 weeks).

safety

Fatigue, anemia, nausea, anorexia and neutropenia were the most common toxic effects (Table 3). Severe grade 3–4 toxic effects were infrequent with fatigue ($n = 6$), anorexia ($n = 5$), nausea ($n = 3$), and diarrhea and leukopenia ($n = 2$ each), being the most common. Two deaths were deemed to be possibly related to study therapy including one non-neutropenic infection and one cerebrovascular hemorrhage, although a definitive causative link could not be established.

quality of life

There were trends toward improvement in the prostate cancer subscale of the QoL ($P = 0.06$) and a general trend toward improvement. However, the small sample size and small proportion of patients returning questionnaires at the end of treatment ($n = 9$) were too limited to make definitive conclusions. Additionally, the high rate of drug discontinuation likely compromised the quality of these data.

discussion

This phase II trial evaluated the safety and activity of single-agent sunitinib (without concurrent corticosteroids) in patients

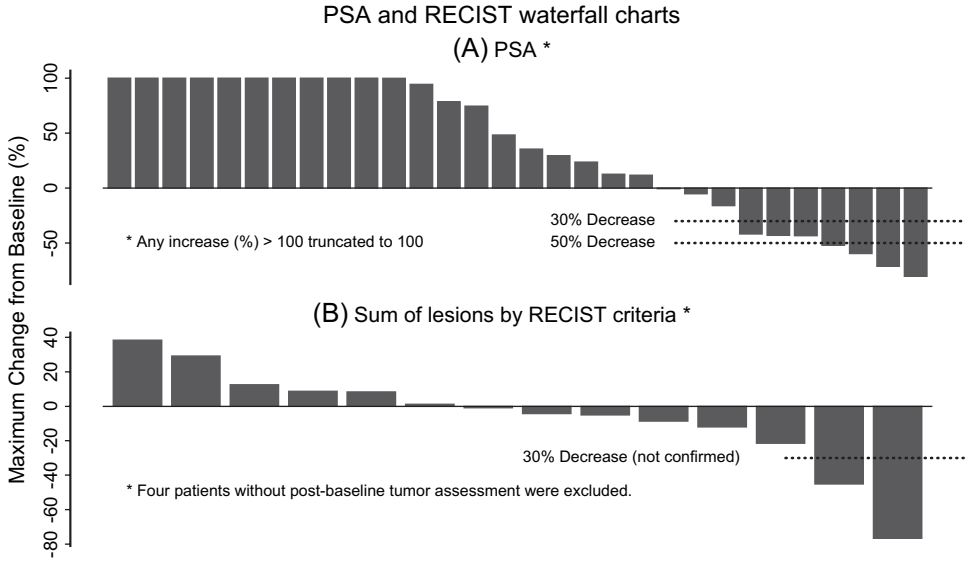

Figure 1. (**A** and **B**) Prostate-specific antigen (PSA) and RECIST waterfall charts.

Table 2. Efficacy of sunitinib

Characteristic	
Clinical PFS ($N = 36$)	
Median (weeks)	19.4
Range	2.6 to 48.3
12-week PFS	75.8%
Overall survival ($N = 36$)	
Median (weeks)	43.7
Range	2.6 to 72.7
6-month (26 week) survival	73.1%
PSA response ($N = 33$), n (%)	
30% decline compared with baseline[a]	7 (21.2)
50% decline compared with baseline	4 (12.1)
Any PSA decline	
Compared with baseline	10 (30.3)
During treatment compared with previous PSA	15 (45.5)
PSA-DT (months) ($N = 28$), median (range)	
At baseline ($n = 28$)	1.4 (0.3 to 24.4)
At end of treatment ($n = 28$)	3.1 (0.4 to 54.6)
Difference between baseline and EOT ($n = 25$)	0.5 (−5.1 to 43.7)
Objective responses (RECIST) ($N = 18$[b]), n (%)	
CR	0
PR	2 (11.1)
Some shrinkage compared with baseline	8 (44.4)
PPI ($N = 22$[c]), n (%)	
At least one decrease <2 points	11 (50.0)
At least one decrease ≥2 points	3 (13.6)
Use of pain medications ($N = 35$), n (%)	
Decreased	6 (17.1)
Increased	7 (20.0)
Remained the same	10 (28.6)
Data incomplete	12 (34.3)
Reason for discontinuation, n (%)	
Progressive disease/recurrence	12 (33.3)
Toxicity[d]	19 (52.8)
Patient request[e]	4 (11.1)
Found to be ineligible/removed	1 (2.8)
Total cycles received	
	2.0
Range	1 to 7
Survival, n (%)	
Alive	18 (50.0)
Dead	18 (50.0)
Cause of death, n (%)	
Disease progression	12 (66.6)
Pulmonary embolism[f]	1 (5.6)
Atrial fibrillation[f]	1 (5.6)
Sepsis[g]	1 (5.6)
Stroke[h]	1 (5.6)
Unknown, no autopsy carried out	2 (11.1)

[a]Includes three patients with 50% decrease; of the four patients previously treated with bevacizumab, one had a >50% PSA decline and one had a 30% PSA decline.
[b]Only patients with baseline measurable lesions included in this analysis and responses were unconfirmed by repeat scanning.
[c]35 patients completed PPI diaries; 22 patients had pain (1–6) at baseline: decreases and increases are measured from baseline.
[d]$n = 1$ each: n/v; pain; pulmonary embolism; sepsis (death); atrial fibrillation (death); taste disturbance and anorexia; bone pain and n/v; pancreatitis; stroke (death); muscle weakness; anorexia and n/v; myalgia and decreased ECOG PS; cellulitis; sepsis, renal failure, and anemia; neutropenia; and drug reaction.
[e]$n = 1$, PSA was rising and patient wanted to stop therapy; $n = 4$ withdrew consent and entered hospice.
[f]Deemed unrelated to treatment and occurred off therapy.
[g]Non-neutropenic, possibly related to treatment.
[h]Possibly related to treatment.
PFS, progression-free survival; PSA, prostate-specific antigen; DT, doubling time; EOT, end of therapy; n/v, nausea/vomiting.

with relatively heavily pretreated patients with metastatic CRPC that had progressed following docetaxel. Additionally, 36.2% of patients had received one other chemotherapeutic agent and 11.1% had also received prior bevacizumab. With the caveat that this is a modest sized phase II trial, the relatively high composite 12-week PFS of 75.8% accompanied by ≥50% and ≥30% PSA declines in 12.1% and 21.2% of patients, respectively, support sunitinib being an active agent in this disease. Although PFS is a soft end point in the setting of metastatic CRPC, it is a relevant end point that dictates clinical decisions. While PSA declines were seen without confirmed PSA responses, these levels of PSA declines appear to be intermediate surrogates for long-term outcomes with chemotherapy [13, 14]. Additionally, of 18 assessable patients, two (11.1%) exhibited an unconfirmed ≥30% tumor shrinkage by RECIST and eight (44.4%) exhibited some reduction in tumor size. In addition, two of the four patients who had received prior bevacizumab displayed a ≥50% PSA decline and a ≥30% PSA decline, suggesting that these agents may not be completely cross-resistant. The phenomenon of PSA elevations coupled with clinical benefit (pain response) observed in other trials with similar TKIs was also noted [16]. Sunitinib administered on a similar schedule has displayed evidence of activity against metastatic CRPC in another phase II trial conducted in the first- and second-line settings with a primary biochemical end point [24]. Sunitinib also appears feasible in combination with docetaxel in the frontline setting for CRPC and when combined with androgen deprivation as neoadjuvant therapy for localized prostate cancer. Additionally, other multitargeted TKIs (sorafenib, AZD2171) have exhibited activity in the setting of CRPC [16, 25–27].

Table 3. Toxic effects in more than one patient

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (%)
Hematological						
Anemia	5	7	1	0		13 (37.1)
Leukopenia	1	2	2	0		5 (14.3)
Neutropenia	2	8	1	0		11 (31.4)
Thrombocytopenia	2	1	1	0		4 (11.4)
Non-hematological						
Alkaline phosphatase increase	2	0	0	0		2 (5.7)
Anorexia	6	2	5	0		13 (37.1)
Cerebrovascular hemorrhage					1[a]	1 (2.8)
Constipation	2	0	0	0		2 (5.7)
Diarrhea	7	4	2	0		13 (37.1)
Edema	2	0	0	0		2 (5.7)
Fatigue	4	6	6	0		16 (45.7)
Hand–foot syndrome	3	0	0	0		3 (8.6)
Hypertension	0	3	0	0		3 (8.6)
Malaise	1	0	1	0		2 (5.7)
Mucositis	7	0	0	0		7 (20.0)
Muscle weakness	1	0	1	0		2 (5.7)
Myalgia	1	0	1	0		2 (5.7)
Nausea	4	5	2	1		12 (34.3)
Peripheral neuropathy	1	1	0	0		2 (5.7)
Rash	5	0	0	0		5 (14.3)
Sepsis					1[a]	1 (2.8)
Stomatitis	1	0	1	0		2 (5.7)
Taste alterations	1	2	0	0		3 (8.6)
Vomiting	1	4	0	0		5 (14.3)
Weight loss	3	1	0	0		4 (11.4)

[a]Cerebrovascular hemorrhage ($n = 1$) and non-neutropenic sepsis ($n = 1$) led to death in two patients; both of these were deemed possibly due to study therapy.

Although most toxic effects were mild, the majority of patients (52.8%) discontinued therapy due to toxic effects. As a result, the median TTF was a more modest 11.8 weeks compared to the median PFS of 19.4 weeks. This elderly population of relatively heavily pretreated patients with metastatic CRPC may tolerate even mild toxic effects poorly compared with younger patients treated in other settings [7, 8]. Closer clinical monitoring and prompt dose reductions for early toxic effects may have mitigated these events. Therefore, the further development of sunitinib in this population warrants careful monitoring for toxic effects and optimal patient selection. Clinical cardiac dysfunction was not observed. However, routine cardiac function monitoring was not carried out due to the low incidence of clinical cardiac dysfunction and the lack of clear relevance of subclinical cardiac dysfunction in a population with advanced malignancy and limited survival.

In conclusion, sunitinib malate displayed activity in the setting of metastatic CRPC following prior docetaxel. Given the high rate of discontinuation of therapy due to toxic effects, a lower dose and less heavily pretreated population may be more optimal. Indeed, an ongoing phase III trial in the second-line setting is comparing sunitinib 37.5 mg daily continuously plus prednisone versus placebo plus prednisone.

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appendix

The following oncologists from US Oncology Network institutions also participated in this study: Rony Abou Jawde, St Joseph, MO; Thomas Boyd, Yakima, WA; Marcus P. Braun, Vancouver, WA; Ernest W. Cochran Jr, Paris, TX; Linda DeMarco, Hudson, NY; Asad Dean, Fort Worth, TX; Tony Ha, Yakima, WA; Stephen M. Hillinger, Albany, NY; Eileen M. Johnston, Edmonds, WA; Edwin C. Kingsley, Las Vegas, NV; Regan M. Look, Portland, OR; Jon K. Minford, Columbia, MD; Ashutosh Rashtogi, Midland, TX; Robert M.

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