A Multi-Institutional Phase II Study of SU101, a Platelet-derived Growth Factor Receptor Inhibitor, for Patients with Hormone-Refractory Prostate Cancer[1]

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ABSTRACT

In a multi-institutional Phase II trial, we evaluated the efficacy of a platelet-derived growth factor receptor (PDGF-r) inhibitor, SU101, in patients with hormone-refractory prostate cancer. The patients received a 4-day i.v. loading dose of SU101 at 400 mg/m^2 for 4 consecutive days, followed by 10 weekly infusions at 400 mg/m^2. The primary study end points were a decline in prostate-specific antigen (PSA) and a decrease in measurable tumor. Secondary end points were time to progression and an effect on pain as measured by the Brief Pain Survey. Expression of PDGF-r was examined in both metastatic and archival primary prostate tumor samples. Forty-four patients were enrolled at four centers. The median age was 72 years, the median PSA was 223 ng/ml, and 21 patients had at least one prior chemotherapy. Thirty-nine patients are evaluable for PSA, and three patients demonstrated a PSA decline >50% from baseline (55–99.9% decrease). The median time to progression was 90 days. Of 19 patients evaluable for measurable disease, 1 patient had a partial response. Nine of 35 evaluable patients had significant improvement in pain. The most frequent adverse events were asthenia (75%), nausea (55%), anorexia (50%), and anemia (41%). PDGF-r expression was detected in 80% of the metastases and 88% of primary prostate cancers. The results of this trial may warrant further clinical studies with other PDGF-r inhibitors.

INTRODUCTION

HRPC[3] is a major cause of mortality and morbidity in men. Although recent clinical trials of taxane-based regimens have demonstrated significant clinical activity in this group of patients (1, 2), no survival benefit has yet been shown with any chemotherapeutic regimen. Therefore, there is a clear need to exploit novel targets and new agents in the search for more effective treatment. Potential therapeutic targets are growth factor receptors that, when stimulated by their cognate growth factors, can result in proliferation of many epithelial malignancies. The largest family of growth factor receptors is the RPTK family. These receptors contain a cytoplasmic tyrosine kinase domain that is autophosphorylated after ligand binding, resulting in a signal transduction cascade that has dramatic effects on cell proliferation and cell survival (3).

To identify potential therapeutic targets, the spectrum of RPTKs expressed in bone marrow metastasis from patients with HRPC has been investigated. Using a reverse transcription-PCR based assay, the PDGF-r-α was found to be the most consistently expressed RPTK (4). Previous studies have shown that both forms of PDGF-r, α and β, are expressed in prostatic intraepithelial neoplasias (5) and adenocarcinomas (6), but not in benign prostate hypertrophy or normal prostatic epithelium. These data suggest that PDGF signaling may be important in the behavior of primary and metastatic prostate cancer.

SU101 is a potent and highly selective inhibitor *in vitro* of PDGF-r-α and PDGF-r-β (7). SU101 minimally interacts with even highly related RPTK receptors, such as epidermal growth factor receptor or fibroblast growth factor receptors. However, SU101 has a short *in vivo* half-life and is converted to its principal metabolite, SU0020, which can inhibit *de novo* pyrimidine synthesis, and, therefore, may possess antiproliferative activity. Nonetheless, in a study of a wide range of tumor xenografts, SU101-induced growth inhibition was significantly greater in tumors that expressed PDGF-r compared with xenografts not expressing this receptor (7). Moreover, during Phase I testing, significant PSA declines (43–93%) occurred in three of five patients receiving SU101 at or near the eventual Phase II dose used in this trial. The major side effects observed

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[3] The abbreviations used are: HRPC, hormone-refractory prostate cancer; RPTK, receptor protein tyrosine kinase; PDGF-r, platelet-derived growth factor receptor; PSA, prostate-specific antigen; KPS, Karnofsky Performance Status; SU101, *N*-[4-(trifluoromethyl)phenyl] 5-methylisoxazole-4-carboxamide; SU0020, *N*-[4-(trifluoromethyl)phenyl]-2-cyano-3-hydroxyl-2-butenamide; BPS, Brief Pain Survey.

in these studies were mild to moderate nausea, vomiting, and fever (8). Therefore, we initiated a multi-institutional Phase II study of this agent based on its preferential inhibition of tumors demonstrating PDGF-r in preclinical analysis, as well as its demonstrated tolerability and activity during Phase I testing. Biopsies of metastatic sites were also obtained, when possible, to assess whether PDGF-r expression correlated with PSA responses. The dose and once weekly schedule was based on the Phase I study, which demonstrated that significant levels of the metabolite SU0020 were achieved and maintained with this schedule.

MATERIALS AND METHODS

Patient Selection. Patients with prostate cancer who had either undergone orchiectomy or were being treated with leutinizing hormone-releasing hormone analogues were eligible. PSA levels were required to be ≥4 ng/ml and to be increasing after a nadir achieved with other active therapies. Evidence of D2 disease (metastatic disease) was not a requirement for study entry. Other eligibility criteria included adequate hematopoietic reserves (absolute neutrophil count >2,000/mm^3, hemoglobin >9.0 g/dl, and platelet count >100,000/mm^3), hepatic function (aspartate aminotransferase, alanine aminotransferase <2.5 times the upper limit of normal, and total bilirubin <1.5 times the upper limit of normal), and renal function (serum creatinine <2 mg/dl). Patients could not be allergic to etoposide and had to have a KPS of ≥60%. Chemotherapy, antiandrogens, immunotherapy, investigational agents, or radiotherapy could not be administered within 4 weeks of beginning the study. Patients on bicalutamide had to undergo a 6-week waiting period to avoid withdrawal responses. Also patients must not have had major surgery within 2 weeks before treatment due to concerns about wound healing. All patients gave written informed consent in accordance with federal, state, and institutional guidelines.

Drug Administration. Patients in this trial were treated with a 4-day loading dose of SU101, followed by 10 weekly infusions. The first treated patient received 200 mg/m^2/day loading and weekly doses. The remaining 43 patients were treated at 400 mg/m^2/day (loading and weekly doses). Patients with objective responses or disease stabilization could continue weekly SU101 treatment for 1 year. After the initial loading dose, no further loading doses were administered with subsequent cycles.

SU101 was supplied by Sugen, Inc. (South San Francisco, CA) in a liquid formulation of 400 mg of SU101 diluted to 10 mg/ml in dehydrated ethanol (26.3%), polysorbate 80 (12.0%), polyethylene glycol (35.0%), citric acid (0.55%), and water for injection (26.2%). The total daily dose was diluted with D5W/0.45% NaCl to a final concentration of 1:15. Infusion bags and tubing were composed of nonpolyvinyl-chloride, nondiethylhexyphthalate materials, and an IMED programmable infusion pump (IMED Corp., San Diego, CA) was used.

Pretreatment and Follow-up Studies. Medical and medication histories, physical examinations, assessment of KPS, and routine laboratory studies were performed before therapy and at week 12. Laboratory studies included a complete blood count, differential, electrolytes, urea, creatinine, glucose, total protein, albumin, calcium, phosphate, uric acid, alkaline phosphatase, total bilirubin, alanine aminotransferase, aspartate aminotransferase, urinalysis, prothrombin time, and partial thromboplastin time. A brief physical examination was performed at the end of the loading dose and at the end of each weekly infusion. Repeat serum chemistries and complete blood counts were obtained after the loading dose on day 4 and before the week 6 infusion. Vital signs were monitored before, 1 h after initiation, and at the end of each infusion. Patients were assessed for toxicity before each weekly infusion.

PSA levels were measured within 7 days before initiating therapy and at weeks 6 and 12. Bone scans were performed at baseline and at week 12. Patients were asked to complete a BPS at baseline and at week 12 of each cycle. Patients with evaluable or measurable disease underwent a computed tomography scan or chest X-ray at baseline and week 12 of each cycle. Before therapy, patients were also asked to consent to a bone marrow biopsy to obtain tumor to evaluate PDGF-r expression in a metastatic lesion.

Immunohistochemistry. Bone marrow biopsies and, in some cases, archival primary prostate tissue including initial core biopsies were analyzed by Labcorp of America (Research Triangle, NC). Immunohistochemical analysis was performed using a rabbit antihuman PDGF-r (α and β) antibody (Upstate Biotechnology, Inc., Lake Placid, NY) diluted at 1:50 in 1% in BSA according to previously published methods (8).

Slides were reviewed by a central pathologist who was blinded to the clinical results of the study. The slides were examined for presence of tumor on a H&E stain before evaluation for immunohistochemical staining for PDGF-r. The presence of PDGF-r staining was scored as: 0, no staining of tumor cells; 1+, weakly positive; 2+, moderately positive; and 3+, strongly positive staining of tumor cells. The percentage of positively staining cells were classified as: <10%, 10–25%, 25–50%, 50–75%, and 75–100%.

Toxicity and Response Criteria. The National Cancer Institute common toxicity criteria were used to grade toxicity. Consistent with the recently published consensus guidelines from the Prostate-Specific Antigen Working Group, a PSA decline of >50% from baseline on two assessments separated by at least 4 weeks was used to determine PSA response (9). PSA progression was defined as a >25% increase over the PSA nadir measured at study entry. For patients with measurable disease, standard response criteria were used. A pain response was defined as a greater than 3-point decline from baseline or a decline to zero on the 10-point BPS scale. Time to disease progression was defined as the period of time on study from the first day of drug administration to the time when disease progression as defined PSA or measurable disease was documented.

RESULTS

Patient Characteristics. From December 1997 to July 1998, 44 patients were enrolled in the study at four tertiary care centers. The characteristics of the patients are listed in Table 1. The median patient age was 72 years, and the median KPS was 80%. All patients were on stable doses of leutinizing hormone-releasing hormone agonists or had undergone bilateral orchiectomy. Eligible patients had to have demonstrated an increasing

Table 1 Patient characteristics

No. of patients	44
Median age	72 (54–84)
Median KPS	80% (70–100)
Median time from diagnosis	4.8 yr (1–19.7)
Prior cytotoxic therapy	48%
Median PSA	203.6 ng/ml (9.7–2949)
Sites of disease	
Bone	89%
Lymph node	41%
Lung	7%
Liver	5%
Analgesic use	
None	20%
Nonnarcotics	23%
Narcotics	57%

PSA within 4 weeks before study entry and values of ≥4 ng/ml. Although the presence of D2 disease was not a requirement for study entry, all patients had evidence of D2 disease, as defined by a positive bone scan and/or radiographic involvement of other sites. Nineteen patients had measurable disease. Twenty-one patients had failed at least one prior chemotherapy. Thirty-five patients were taking analgesics on a prescribed, regular basis, and 22 patients required narcotic analgesics.

PSA Response. Of the 44 patients enrolled, 39 were evaluable for PSA response. The remaining five patients had stable PSA values at week 6 but did not have a follow-up assessment and are not evaluable. Of the remaining 39 evaluable patients, 3 had significant declines in their previously rising PSA measurements while undergoing SU101 treatments. One patient demonstrated a dramatic PSA decline with an entry PSA of 293 ng/ml that declined to 0.3 ng/ml by week 12. Two other patients had PSA declines of 63% and 55% from baseline. Ten additional patients had stable PSA (defined as a <25% increase) during the course of the 12-week therapy cycle. Thus, 3 of 39 (8%) had PSA reductions ≥50%, and a further 10 of 39 (26%) had stabilization of their previously increasing PSAs.

Measurable or Evaluable Disease Response. Nineteen of the 44 patients (43%) had radiographically measurable disease. Eleven of these 19 patients did not have follow-up scans at the discretion of the treating physician or due to patient request. Of the eight patients with follow-up scans, one had a partial response (lung and nodal metastasis) and three had stable disease (one with lung lesions, one with lymph node disease, and one with pelvic wall metastasis). Thus, in the patients with measurable lesions, 4 of 19 (21%) had tumor responses or disease stabilization while being treated with SU101.

Thirty-nine patients had evidence of metastatic disease on baseline bone scans. Twenty-eight patients had a follow-up scan and were evaluable. Of the 28 evaluable patients, 4 (14%) had scans that improved and 14 (50%) had scans that stabilized on SU101.

Pain Response. Patients were assessed for a subjective improvement in pain using the BPS at baseline, week 12, and at time of early withdrawal. Of the 44 patients enrolled in the study, 35 reported pain at the baseline assessment and 21 of these completed at least one follow-up assessment. Of these 21 patients, 9 (43%) had a ≥3-point decline or decline to zero on a 10-point scale. Eight of these patients remained on stable doses of pain medication while one patient was able to lower his dose of pain medication. Seven additional patients reported that their pain symptoms stabilized, and five patients reported worsened pain. Therefore, the overall pain response rate was 9 of 35 (26%) patients, and an additional 8 of 35 (23%) patients had stabilization of their pain.

Immunohistochemistry for PDGF-r. Thirty-one patients underwent a bone marrow biopsy at baseline, and 35 samples were obtained (four patients with two samples each). Fifteen of these samples (43%) contained tumor by routine histology (Table 2). From the samples with tumor present in the bone marrow, 80% (12 of 15) were positive for PDGF-r staining. In addition to the metastatic marrow samples, one sample from a metastatic lymph node from the neck demonstrated 1+ staining. For example, patient 17 had both an archival prostate needle biopsy and a bone marrow biopsy with tumor present for immunohistochemical analysis (Fig. 1).

To compare PDGF-r expression in the metastatic hormone-refractory and primary tumors, 28 archival primary prostate tissues were obtained from 24 patients (4 patients with two samples each). Five samples did not contain any tumor. The percentage of positive PDGF-r staining in primary prostate tissue was 88% (20 of 23). Lymph node tissue from patient 31, who experienced a >50% decline in PSA, demonstrated 1+ staining in 50–75% of the tumor cells. The primary prostate tumor tissue in patient 36, who also experienced a >50% PSA decline, also had 1+ staining in 25–50% of tumor cells. No metastatic tumor tissue was available in this patient nor in the third patient who had a significant PSA decline.

Toxicity. A total of 615 infusions were delivered to 44 patients. Twenty-nine patients completed 12 weeks of therapy (one cycle). Ten of 44 (23%) patients were withdrawn for adverse events (asthenia, $n = 3$; thrombocytopenia, $n = 2$; exfoliative rash, $n = 1$; anxiety, $n = 1$; altered mental status, $n = 1$; methemoglobinemia, $n = 1$; gastrointestinal bleed, $n = 1$). The most common adverse events were asthenia, nausea, anorexia, and anemia (Table 3), which were from mild to moderate in severity. The most common severe (grade 3 or higher) adverse events were asthenia, anemia, and pain. Altered mental status was seen in seven patients. Other toxicity included grade III methemoglobinemia ($n = 1$), grade III exfoliative rash ($n = 1$), and hypertension during drug infusion ($n = 1$). Neutropenia was uncommon; and grade 3 thrombocytopenia was observed in only two patients. There were two deaths while on study; one due to pulmonary hypertension and a death in another patient who suffered an acute cerebral vascular accident. Neither of these two events was attributed to SU101.

Time to Progression and Survival. The median time to progression equaled 90 days for the 44 patients enrolled in the study. Twenty-nine patients completed at least one cycle of treatment. One patient completed a total of five cycles over the course 15 months. The median survival for patients in this study was 342 days (11.2 months).

Table 2 Immunohistochemistry results for patients with tumor present

Patient	Prostate primary	% positive cells	Bone marrow metastasis	% positive cells
1[a]	1+/0	10–25%	0	NA[b]
7	NS	NA	0	NA
8	NS	NA	2+	75–100%
9	0	NA	0	NA
10	NS	NA	2+	50–75%
11	3+	75–100%	1+	10–25%
12	NS	NA	1+	50–75%
13[c]	1+	75–100%	1+/0	<10%
14	NS	NA	1+	10–25%
15	2+	75–100%	NS	NA
17	1+	10–25%	2+	75–100%
18	1+	25–50%	1+	75–100%
20	1+	25–50%	NS	NA
21	1+	25–50%	NS	NA
22	1+	10–25%	1+	10–25%
24	NS	NA	1+	10–25%
25	0	NA	NS	NA
28	1+	<10%	NS	NA
29[a]	3+/2+	75–100%/75–100%	NS	NA
31[d]	NS	NA	1+ (node)	50–75%
32[a]	1+/2+	75–100%/25–50%	NS	NA
33	1+	10–25%	NS	NA
36	1+	25–50%	NS	NA
37[a]	2+/2+	50–75%/75–100%	NS	NA
39	1+	10–25%	NS	NA
40	1+	<10%	NS	NA
42	NS	NA	1+	75–100%

[a] These patients have two separate tissue blocks from their prostates.
[b] NA, not applicable; NS, no sample.
[c] This patient had two bone marrow biopsies.
[d] This sample is from a lymph node.

DISCUSSION

Inhibition of growth factor signaling, such as the PDGF pathway, may be a useful strategy in treating patients with advanced malignancies. PDGF is a potent growth factor and the product of an established viral oncogene (v-*sis*). Its receptor, PDGF-r, has been found to be activated by a fusion to the transcription factor TEL (10) in a subset of patients with chronic myelomonocytic leukemia. An autocrine pathway involving PDGF-r has also been implicated in growth of solid tumors such as glioblastoma (11). On the basis of previous reports of PDGF-r expression in prostate cancer, we investigated the effects of the only available PDGF-r inhibitor, SU101, in patients with metastatic HRPC. This clinical trial included an assessment of PDGF-r expression in both metastases and archival primary prostate specimens.

SU101 administered as a single agent according to the described schedule resulted in only a modest overall objective clinical benefit in these heavily pretreated patients. One patient with measurable disease exhibited a marked reduction in lymph node size and PSA (from 293 ng/ml to 0.3 ng/ml). However, except for four patients who demonstrated an improvement in pretreatment bone scans, there were no other patients who demonstrated objective tumor regression. An additional two other patients demonstrated significant (>50%) reductions in their pretreatment PSA values.

Because declines in PSA are not necessarily correlated with clinical benefit, we examined the effect of SU101 on pain as measured by the BPS. The percentage of patients (26%) who reported improvements in pain was higher than that seen for either decreases in PSA or measurable disease. Because this was not placebo-controlled trial, it is possible that the amelioration of pain reported by some patients represented a placebo effect. However, we cannot exclude a direct palliative effect from this agent or its metabolite.

In contrast to the rate of disease regression, a greater percentage of patients in this study demonstrated stable measurable disease (16%) or stable PSA values (26%) during at least the initial 12-week cycle. Although the stable disease categorization has not been shown to correlate with a clear-cut survival advantage in HRPC studies, it may be of use in evaluating selective new agents such as SU101. Inhibition of growth factor pathways, such as with the antibody against the epidermal growth factor inhibitor, often results in cytostatic effects *in vitro* (12). Therefore, for agents that inhibit growth factor signaling, PSA decline as a clinical end point may be less informative. For future trials with agents that are potentially cytostatic, time to PSA progression may be a more appropriate end point than PSA decline.

SU101 administered according to the described schedule was only moderately tolerated. The most frequent side effect in this patient population was asthenia (Table 1). The asthenia observed in this study was not unexpected, given the advanced age, extensive prior chemotherapy, and extent of disease in this patient population. We also noted that a treatment interruption of 1 or 2 weeks resulted in greater patient tolerability. Nausea was the second most common side effect, but was grade 1 in most patients and was easily managed with standard antiemetics. There was no significant leukopenia, although moderate anemia was noted in the majority of patients. Poor bone marrow reserve due to disease infiltration is common in this group of patients and may have contributed to the anemia observed.

The median survival in this group of patients was 11.2 months. Although survival was not a primary objective of the study, this figure is consistent with recent clinical trials in HRPC. For instance, in a similar patient population, combination therapy with etoposide, paclitaxel, and estramustine (2) or mitoxantrone and hydrocortisone (13) demonstrated similar median survivals of 12.8 months and 12.3 months, respectively.

One possible explanation for the low response rate in this study is that the short half-life of SU101 leads to only transient blockade of PDGF-mediated signaling and that a more prolonged receptor inhibition may be necessary for clinical benefit. However, it is not clear that any of the antitumor effects observed in this study result only from inhibition of PDGF signaling. SU0020, the major metabolite of SU101, interferes with pyrimidine synthesis and has a longer half-life than the parent drug. However, *in vitro* studies with SU101 have demonstrated selectivity for the PDGF-r pathway independent of pyrimidine synthesis (7). Also, in animal studies, xenografts expressing PDGF-r demonstrate greater SU101-induced growth inhibition than xenografts with minimal or no PDGF-r expression, suggesting a PDGF-r-mediated mechanism of action (7).

To date, studies of PDGF-r expression in human prostate cancer have only included the primary sites in one study (6) or

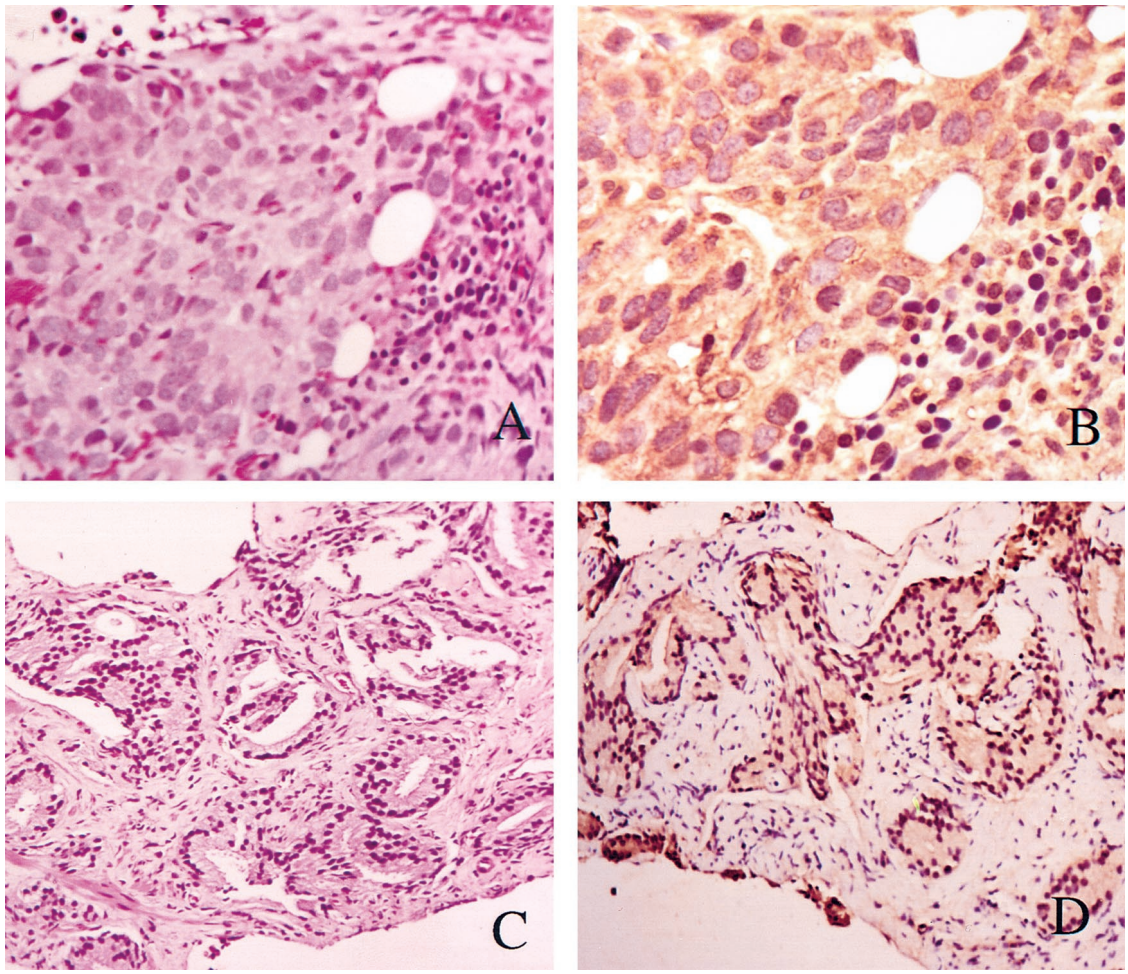

Fig. 1 Immunohistochemical analysis of tumor samples from patient 17. *A*, H&E stain of bone marrow biopsy at ×40 magnification. Focus of normal bone marrow elements on the *right* of the photograph, and focus of metastatic prostate adenocarcinoma on the *left*. *B*, immunoperoxidase stain for PDGF-r in bone marrow biopsy. Graded as 2+ in 75–100% of cells (×40 magnification). *C*, archival prostate needle biopsy. H&E stain at ×20 magnification. *D*, immunoperoxidase stain for PDGF-r in prostate biopsy. Graded as 1+ staining in 10–25% of cells (×20 magnification).

Table 3 Most frequent adverse events

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Asthenia	11%	39%	27%	2%
Nausea	41%	14%	2%	
Anorexia	23%	25%	5%	
Anemia	5%	27%	25%	2%
Vomiting	25%	11%		
Diarrhea	34%	2%		
Back pain	18%	5%	7%	
Pain	11%	9%	5%	
Fever	14%	11%		
Dyspnea	16%	7%		

a limited number of metastasis in another (4). This is the first study in which PDGF-r expression has been studied both in the primary and the metastatic setting. The level of PDGF-r expression did not differ between the primary and metastatic sites, even for samples obtained from the same patient. Therefore, although the metastatic sample was often obtained years after removal of the prostate gland, the level of PDGF-r staining was not substantially different (Table 2). These findings suggest that the PDGF-r is consistently expressed during disease progression and may be a therapeutic target for all stages of disease.

In summary, the effects of SU101 alone in this population of HRPC patients are modest. Nonetheless, given the presence of the PDGR-r in metastatic prostate tumor samples, these results suggest that studies with other PDGF-r inhibitors, either alone or in combination with cytotoxic agents, may be warranted. For future trials, the ability to assess the activation (phosphorylation) status of the PDGF-r or its downstream targets either in tumor or surrogate tissue will greatly enhance the ability to correlate efficacy at both the molecular and therapeutic levels.

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