

Platelet-Derived Growth Factor Receptor Inhibitor Imatinib Mesylate and Docetaxel: A Modular Phase I Trial in Androgen-Independent Prostate Cancer

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ABSTRACT

Purpose

To study the platelet-derived growth factor receptor (PDGFR) inhibitor imatinib mesylate in androgen-independent prostate cancer (AIPC), alone and in combination with docetaxel, we designed a modular phase I trial. Our goals were to (1) evaluate the toxicity and maximum-tolerated dose of docetaxel with imatinib, and (2) evaluate the decline of prostate-specific antigen (PSA) induced by imatinib alone, and imatinib and docetaxel.

Patients and Methods

Twenty-eight men with AIPC and bone metastases were enrolled to receive imatinib 600 mg daily lead-in for 30 days, then imatinib 600 mg daily and one of six possible doses of docetaxel weekly for 4 weeks every 6 weeks.

Results

During the imatinib lead-in module, one dose-limiting toxicity (DLT) event was observed, while two (7%) of 28 had PSA decline (both < 50%). With imatinib and docetaxel, cycle 1 DLT was found in three of 12 patients at docetaxel 30 mg/m², in three of four patients at docetaxel 45 mg/m², and in five of six patients at docetaxel 35 mg/m². DLTs (n = 40 total events) were principally fatigue (35%) and nausea (20%). Eight (38%) of 21 had PSA decline greater than 50%, and six (29%) of 21 had PSA decline less than 50%. Serial PSA declines beyond 18 months were observed. PDGFR-expressing tumor declined on serial bone marrow biopsies with combination therapy alone.

Conclusion

With imatinib 600 mg daily, the maximum-tolerated dose of docetaxel was determined to be 30 mg/m² weekly for 4 weeks every 6 weeks. Long-term responses were observed. The role of imatinib in modulating outcomes to docetaxel in AIPC is being tested in a randomized phase II trial.

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INTRODUCTION

Although chemotherapy yields consistent palliative responses in metastatic androgen-independent prostate cancer (AIPC), the overall survival duration is limited.^{1,2} Mechanisms of disease progression have suggested additional therapeutic targets. The bone microenvironment is a preferred site for prostate cancer metastases; the bone-epithelium interaction results in a metastatic phenotype that is highly conserved and characterized clinically by osteoblastic lesions. The burden of metastases in bone

largely defines the symptoms of metastatic prostate cancer and serves as an independent prognostic marker for survival.³ Radioisotope-based targeting of bone metastases in prostate cancer may prolong survival,⁴ suggesting that a bone-directed approach may alter the natural history of the disease.

Several lines of evidence implicate the platelet-derived growth factor receptor (PDGFR) in prostate cancer progression in bone. PDGFR is a transmembrane tyrosine kinase receptor that is overexpressed in the majority of bone metastases from prostate

cancer,^{5,6} as well as in primary prostatic adenocarcinomas.^{7,8} Prostate cancer cells also express the receptor ligand PDGF,⁸ a known mitogen for osteoblasts, and this could contribute to the striking osteoblastic phenotype. Autocrine and paracrine signaling via the PDGFR may, therefore, play a role in the pathophysiology of prostate cancer progression in bone. These lines of evidence led us to study the therapeutic potential of PDGFR inhibition in vivo in an animal model of prostate cancer bone metastases. The results of these studies demonstrated that the PDGFR inhibitor imatinib mesylate (STI571, Gleevec; Novartis Pharmaceuticals, East Hanover, NJ),⁹ in combination with taxane therapy, had greater antitumor efficacy than either agent alone.¹⁰

We felt that the finding worthy of validation was that the combination of a taxane and PDGFR inhibition was superior to PDGFR inhibition alone in tumors expressing PDGFR. To efficiently study the effect of a PDGFR inhibitor in prostate cancer, alone and in combination with cytotoxic therapy, we designed a modular phase I trial. Its purpose was to characterize the toxicity of imatinib alone and of the combination of imatinib plus docetaxel, and to obtain a preliminary screen of efficacy of imatinib alone and imatinib plus docetaxel. By serially treating each patient with single-agent imatinib followed by the combination, we assessed the toxicity and modulation of prostate-specific antigen (PSA) for each module of therapy.

PATIENTS AND METHODS

Patient Selection

Men with progressive AIPC and bone metastases were eligible for this study. All patients had progressive disease by clinical, radiological or PSA-based criteria. PSA progression was defined as two consecutive rises in the PSA level of at least 1 ng/mL over 4 weeks. When relevant, withdrawal of antiandrogen therapy was required. Patients had an Eastern Cooperative Oncology Group performance status of 2 or better, a serum testosterone level \leq 30 ng/dL, and were maintained on luteinizing hormone-releasing hormone (LHRH) agonist therapy. Adequate organ functions were required and were defined as an absolute neutrophil count \geq 1,500/mm³, platelet count \geq 100,000/mm³, serum bilirubin \leq 1.5 mg/dL, AST and ALT \leq 2 \times the upper limit of normal, serum creatinine clearance \geq 40 mL/min, or serum creatinine less than 1.5 \times the upper limit of normal. Patients with comorbidities including symptomatic congestive heart failure, unstable angina or recent myocardial infarction, and oxygen-dependent lung disease were excluded. Chemotherapy or radiation therapy within the last 30 days and systemic radioisotope therapy within the last 90 days were not permitted. All patients gave written informed consent according to federal and institutional guidelines.

Dosage and Drug Administration

Lead-in period. Patients were treated initially with imatinib mesylate at 600 mg daily in single or divided doses, for 30 days. Tolerance and compliance were assessed during and at the end of the lead-in. Patients who took \geq 80% of the prescribed drug were

eligible for combination therapy. Imatinib capsules were supplied by Novartis Pharmaceuticals.

Combination therapy. Patients eligible to proceed to combination therapy received intravenous docetaxel, at one of six possible doses, weekly for 4 consecutive weeks (days 1, 8, 15, and 22) every 6 weeks as outpatients. Oral steroid premedication for docetaxel was dexamethasone 10 mg, 12 and 2 hours before docetaxel, and 8 hours after docetaxel. Oral imatinib was continued at 600 mg daily for the full 6 weeks. Patients were enrolled in cohorts of six. The six potential docetaxel dose levels were 20, 25, 30, 35, 40, or 45 mg/m² weekly.

Statistical Design

Dose finding for docetaxel was performed using the continuous reassessment method (CRM).¹¹ Patients were treated in cohorts of six; as many eight cohorts were possible. The first cohort was treated at 30 mg/m². Fixed probabilities of toxicity ($p_1, p_2, p_3, p_4, p_5, p_6$ equalling 0.07, 0.16, 0.30, 0.40, 0.46, 0.53, respectively) were used for implementing the CRM under the model

$$\text{prob}[\text{dose-limiting toxicity/dose level } j] = p_j^{\text{exp}(a)}$$

with the parameter "a" following a Gaussian prior with mean 0 and variance 2. The fixed probabilities were selected based on the basis of assumptions derived from clinical experience. Patients who could not be assessed for toxicity during the combination therapy because of dropout during the lead-in period or early combination therapy period were replaced. The maximum-tolerated dose (MTD) was defined a priori as the dose level of docetaxel in combination with oral imatinib at 600 mg daily that achieved a dose-limiting toxicity (DLT) rate closest to 30%. For implementing the CRM, the definition of DLT was any toxicity that resulted in a delay of 1 week or more in the administration of either docetaxel or imatinib during the combination module of the study. Similarly, any toxicity that resulted in a dose-reduction during the combination module of the study was defined as DLT. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (Version 2.0).

Dose Reductions

Dose reductions by one level (both drugs) were permitted for intolerable nonhematologic grade 2 toxicity or any grade 3 or 4 toxicity after both drugs were held and toxicity resolved or improved to grade 2 or less. Recurrent toxicity of similar severity would result in another dose reduction by one level, but patients requiring more than two dose reductions or any delay by 2 weeks or more in scheduled therapy as a result of toxicity were withdrawn from the study. Successive dose levels for imatinib, if dose reduction was required, were 400 mg (level 1) and 300 mg (level 2) daily, respectively. All patients were required to have absolute neutrophil counts greater than 1,500/mm³ and platelet count more than 75,000/mm³ for treatment on D1 of each cycle of combination therapy.

Pretreatment and Follow-Up Studies

Historical data collected on each patient included performance status, prior cancer therapy, current medications, and a Brief Pain Inventory. Physical examination and routine laboratory evaluations, including PSA, were performed. A bone scan and computed tomography scan of the abdomen and pelvis were required. Serial unilateral bone marrow biopsies from the posterior superior iliac crest were obtained in consenting patients at baseline and at the start of the first two cycles of combination therapy.

PDGFR immunohistochemistry (goat anti-PDGFR-b, goat anti-phospho-PDGFR-b; Santa Cruz Biotechnology Inc, Santa Cruz, CA) was performed on sections from decalcified and paraffin-embedded bone biopsy specimens. Radiological studies were repeated after every two cycles of combination therapy or to evaluate symptoms or signs of progressive disease. Weekly monitoring during combination therapy included weight, CBCs, liver function tests, and creatinine.

Definition of Treatment Outcomes

PSA-defined partial response to therapy was defined as a decline in PSA level by $\geq 50\%$ of entry level value (before lead-in), sustained for at least 8 weeks. Partial response in measurable disease was defined as 50% reduction in the products of the diameters of all index lesions in patients with measurable disease, sustained for at least 8 weeks. Progressive disease was defined as three consecutive increases in PSA level by at least 1 ng/mL, the first value $\geq 25\%$ above nadir or baseline, measured at least 2 weeks apart; any increase greater than 25% in the products of diameters of any measurable lesion; or the appearance of an unequivocally new lesion. Whenever possible, patients received at least two cycles of combination therapy before a designation of progression was made. Time to progression was measured from the time of entry into protocol to the earliest of signs or symptoms secondary to progressive disease, radiological progression, or, if defined by PSA level alone, the time to first of three consecutive PSA elevations above 125% of the nadir or baseline PSA value. Patients were removed from the study for unacceptable toxicity, noncompliance, refusal to continue therapy, or progressive disease.

RESULTS

General

Twenty-eight men were enrolled. Patient characteristics presented in Table 1 indicate a heavily pretreated and largely symptomatic group of patients.

Lead-In Period With Imatinib Alone

Toxicity. Only one DLT event was encountered during lead-in among the 28 patients enrolled in the study,

experienced by a patient with transient acute renal failure secondary to acute tubular necrosis. This event was attributed to imatinib, and the patient was removed from the study.

PSA outcomes. Of 28 patients enrolled onto the study, 24 completed the lead-in period. Three patients were removed from the study within the first 2 weeks because of rapid disease progression, characterized by debilitating bone pain and fatigue. By the end of the lead-in period, two patients had PSA declines less than 50%, and the remainder had increases in PSA levels from baseline (range, 1.03 to 7.8-fold; median, 1.8-fold). Sixteen patients (67%) had a PSA increase greater than 50% from the baseline value. Changes in measurable disease were not assessed. No reductions in imatinib dose were necessary. By the end of the lead-in period, all remaining 24 patients were eligible to proceed to combination therapy.

Docetaxel and Imatinib (cycle 1) Toxicity

Of the 24 patients who received combination therapy, 21 completed one cycle of therapy and were assessable for response. Three patients were removed from the study during the first cycle of therapy and could not be assessed for response—one, for rapid progression after receiving only one dose of docetaxel; one, for toxicity (grade 3 fatigue) after three doses of docetaxel; and a third, for accelerated angina requiring emergent coronary artery bypass graft surgery.

The rates of first-cycle DLTs per cohort, which were the basis for the CRM dose-finding algorithm, are presented in Table 2. Because the trial design allowed dose-levels to be skipped while escalating, the absence of any DLTs (0 of six patients) at the starting dose level (30 mg/m²) led to assignment of 45 mg/m² to the second cohort. However, the observation of excessive toxicity (three of four patients with DLT) at the 45 mg/m² dose level led us to curtail enrollment of the second cohort early, at four patients, and recompute the posterior distribution based on the data from these first 10 patients, rather than 12. This led the CRM to assign 35 mg/m² as the next dose level for the third cohort of six patients. Per the CRM, the fourth cohort was treated at a dose level of 30 mg/m², and based on the toxicity data at that point, it was then decided to terminate the trial. The

Table 1. Patient Characteristics

	Patients (N = 28)	
	No.	%
Age, years		
Median	66	
Range	44-81	
ECOG performance score 1-2	18	64
Prior taxane therapy	15	55
Prior chemotherapy	26	93
≥ 2 prior chemotherapy regimens	19	68
Prior external beam radiation therapy	15	54
Prior radioisotope therapy	8	29
Elevated alkaline phosphatase	15	54
Elevated lactate dehydrogenase	9	32
Hemoglobin < 11 g/dL	5	18

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Cohort Sequence With First-Cycle DLT

Cohort No.	Dose Level (mg/m ²)	First-Cycle DLTs	
		Proportion	%
1	30	0/6	0
2	45	3/4	75
3	35	5/6	83
4	30	3/6	50

Abbreviation: DLT, dose-limiting toxicity.

Table 3. Quantitative Toxicity of Combination Therapy

Cohort (dose level [mg/m ²])	No. of Patients		Patient Cycles (total per dose level)	Patients With DLT (proportion)	
	Starting Level	Reduced Level*		Cycle 1	All Cycles
20	0	2	2	0/2	0/2
25	0	9	19	0/9	2/9
30	12	3	40	4/15	9/15
35	6	1	13	5/7	6/7
40	0	3	4	1/3	2/3
45	4	0	4	3/4	3/4

Abbreviation: DLT, dose-limiting toxicity.

*Includes reductions of imatinib dose.

cumulative DLT rates for all patients per dose level are presented in Table 3 and include toxicity experience in later cycles, including those DLTs observed after dose reductions. Using a first-cycle DLT rate closest to 0.3 to define the MTD, we estimated the MTD for docetaxel as 30 mg/m² weekly for 4 weeks, in 6-week cycles in combination with 600-mg imatinib daily.

Hematologic and Nonhematologic DLT

Of the 24 patients who received combination therapy, 15 (62%) experienced at least one episode of DLT. These single or cluster DLT events (n = 40) are enumerated in Table 4. DLTs were principally grade 2 (42%) or grade 3 (55%) in severity. Only one patient had therapy held for a week (for grade 2 neutropenia) before a dose reduction was employed. No other hematological DLT was noted. Nonhematologic DLTs, principally nausea (20%) and fatigue (35%), were the major DLTs experienced. Diarrhea and edema syndromes were less frequent. Most DLTs were managed successfully with interruption of therapy until recovery followed by single dose-level reductions in both docetaxel and imatinib. Of four patients removed from the

study for DLT, two went off study without a dose reduction implemented—one, after only one dose-level reduction, and one, after two dose-level reductions. One patient experienced grade 3 noncardiogenic pulmonary edema at the docetaxel 35 mg/m² level. After treatment with steroids and diuretics, he fully recovered. The only grade 4 toxicity was exfoliative dermatitis (docetaxel at 45 mg/m² level). No deaths attributable to toxicity occurred. No unexpected adverse events were encountered.

PSA and Disease Outcomes With Combination Therapy

Of 21 patients completing one cycle of combination therapy, five (24%) achieved a \geq 50% reduction in entry-level PSA (of these, three achieved a \geq 80% reduction). Of these five patients, two had measurable disease—one patient with nodal disease had a partial response and another with nodal and liver disease had a minor response. One patient's disease has since progressed and all others remain on therapy without disease progression; the progression-free period is now beyond 18 months for two patients. The median time from study entry to PSA decline by 50% was 150 days (range, 100 to 240 days). PSA fluctuations during therapy were not uncommon, as seen in the example in Figure 1. The median duration of PSA response for these patients has not been reached and is currently 8 months;

Table 4. Qualitative Toxicity of Combination Therapy

Type of DLT	Grade of DLT Event (No. of events)			DLT Events	
	2	3	4	No.	%
Nausea	5	3	0	8	20
Vomiting	2	1	0	3	8
Diarrhea	0	4	0	4	10
Pulmonary edema	1	1	0	2	5
Fatigue	4	10	0	14	35
Anorexia	1	1	0	2	5
Weight loss	3	0	0	3	8
Rash	0	0	1	1	2
Neutropenia	1	0	0	1	2
Visual changes	0	1	0	1	2
Hematuria	0	1	0	1	2
Total	17	22	1	40	100

Abbreviation: DLT, dose-limiting toxicity.

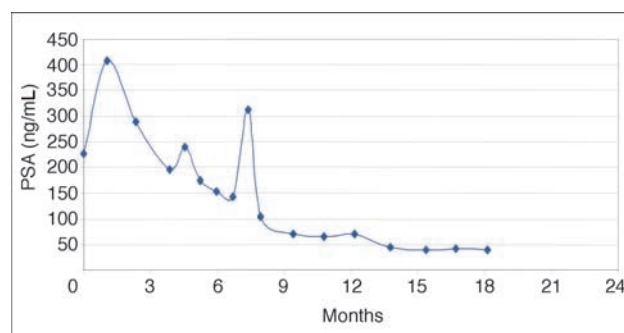


Fig 1. Prostate-specific antigen (PSA) fluctuations noted in a long-term responder to combination therapy. The first 30 days are on imatinib alone.

Treatment	PSA Reduction > 50%	PSA Reduction < 50%	PSA Increase
Imatinib* for 30 days			
Proportion	0/28	2/28	25/28
%	0	7	89
Docetaxel plus imatinib			
Proportion	8/21	6/21	7/21
%	38	29	33

Abbreviation: PSA, prostate-specific antigen.
 *One patient was not assessable for PSA outcome (off study for toxicity).

similarly, the median progression-free survival duration is 11 months.

Of the 21 patients who received at least one cycle of combination therapy, 14 (67%) experienced PSA declines from the end of the lead-in period; eight (38%) had PSA decline greater than 50%. One of these latter eight patients had progressive disease after lengthy docetaxel therapy before study entry. After experiencing an increase in PSA and bone pain during the lead-in period, he received marked palliative improvement in bone pain on combination therapy. PSA outcomes for each module of therapy are summarized in Table 5.

Of the 21 patients who received at least one cycle of combination therapy, eight (38%) had measurable disease. One patient had a partial response; one, a minor response; three, stable disease; and two had progressive disease. One patient was not evaluated but had experienced progression by other criteria.

Altogether, of the 28 patients who were registered, five remain on treatment, five were removed from study for toxicity, one had an intercurrent event unrelated to therapy, and 17 had progressive disease. Time to progression from study entry varied from 2 weeks to 10 months (median, 2 months). To date, 20 patients (71%) remain alive with a median follow-up duration of 10 months.

Pain Outcomes

Pain scores (range, 0 to 10) from the Brief Pain Inventory were tabulated at baseline, after imatinib alone, and after one cycle of combination therapy. The mean worst pain score rose to 3.75 (range, 0 to 10) after imatinib, compared with 2.0 (range, 0 to 6) at baseline. Similarly the mean average pain score rose to 2.5 (range, 0 to 6) from 1.4 (range, 0 to 3). With combination therapy, the mean worst pain score fell to 1.3 (range, 0 to 4), and mean average pain, to 1.0 (range, 0 to 3). In all cases, pain was of bony origin.

Analysis of PDGFR Status in Bone Lesions

Serial bone marrow biopsies were performed in eight patients at baseline, after the lead-in period with imatinib alone, and after cycle 1 of combination docetaxel plus imatinib. Of these eight, two had serial bone marrow specimens

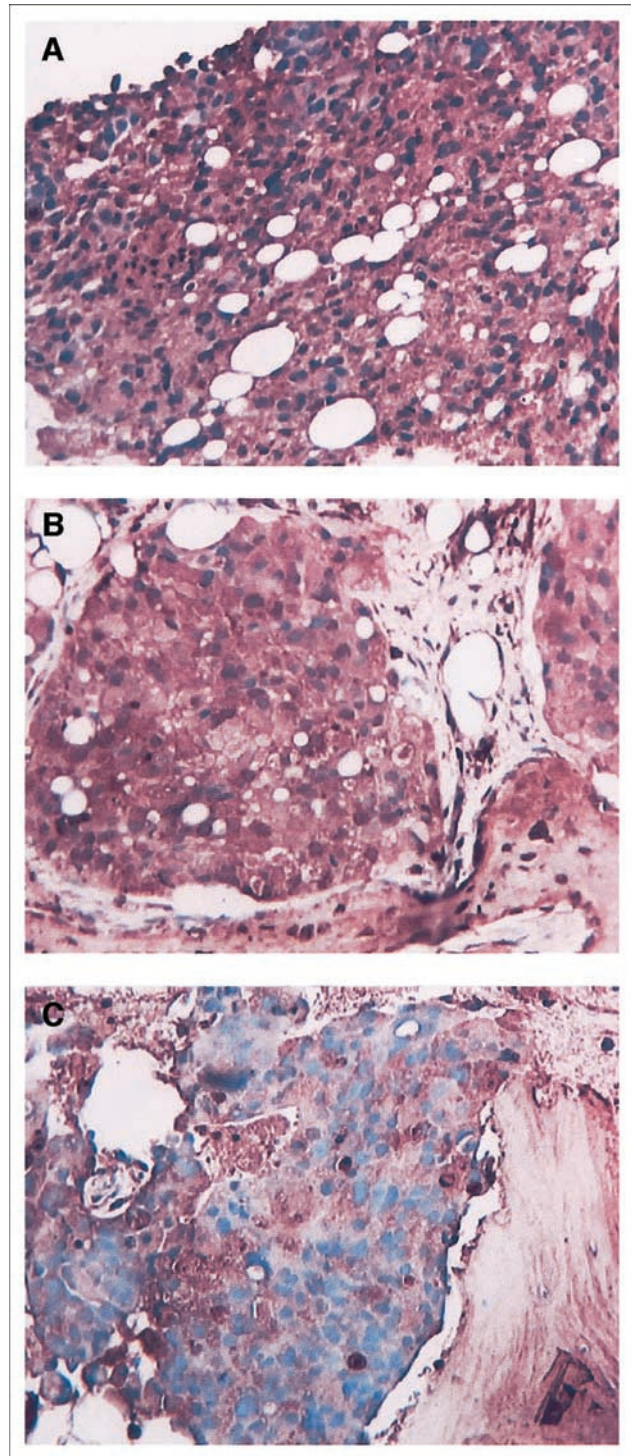


Fig 2. Platelet-derived growth factor receptor expression in bone marrow biopsies from a patient at (A) baseline, (B) after 30 days of imatinib therapy, and (C) after one cycle of imatinib plus docetaxel therapy.

with tumor that was amenable to serial PDGFR and phospho-PDGFR staining. As shown in the example in Figure 2, there was no readily discernible change in PDGFR expression from baseline (Fig 2A) with imatinib alone (Fig

2B). With combination therapy, however, the percentage of tumor expressing PDGFR declined markedly (Fig 2C). No differences between tumor expression of PDGFR and phospho-PDGFR were noted. In this patient, the decline in percentage of tumor expressing PDGFR was associated with a decline in PSA level after combination therapy, whereas the PSA level rose during lead-in with imatinib alone.

DISCUSSION

The goals of this phase I trial were to examine the feasibility of combining the PDGFR inhibitor imatinib mesylate and docetaxel in men with AIPC, and to gain preliminary insight into the likely activity of imatinib alone, and imatinib and docetaxel in this disease setting. We observed no meaningful evidence of antitumor activity in AIPC after daily administration of the potent PDGFR inhibitor imatinib mesylate for 30 days as measured by PSA decline by 50%, or improvement in pain. Whereas the toxicity with imatinib alone was minimal, the mean PSA level increased by almost two-fold, accompanied by a similar increment in pain indices. A previous single-agent phase II clinical trial in AIPC that studied intermittent intravenous administration of a weak PDGFR inhibitor with a short half-life showed negligible clinical activity.⁶ This result led to speculation that the transience of the inhibition of the PDGFR pathway may have been responsible for the lack of effectiveness. While categorical conclusions cannot be drawn, these outcomes at 30 days have led our group to the estimation that the daily administration of a potent PDGFR inhibitor, imatinib mesylate, is ineffective in AIPC, and we have chosen not to study it further, as a single agent, in the phase II setting.

The combination of daily imatinib at 600 mg and a weekly regimen of docetaxel for 4 of 6 weeks at 30 mg/m² was initially well tolerated by most patients, while up to 60% required dose-reductions eventually. Nevertheless, we showed that chronic combination therapy over 18 months is feasible in patients who are both free from progressive disease and significant cumulative toxicity. A marked increase in first-cycle DLT rate was noted at higher doses. Further studies are needed to clarify whether a drug interaction was responsible for this finding.

During combination therapy, hematological toxicity proved trivial in this heavily pretreated group of patients, and nonhematological toxicity, principally nausea and fatigue, dominated the DLT picture. At least one source of potentially life-threatening toxicity with this regimen is noncardiogenic pulmonary edema or pneumonitis. Chronic fatigue and nausea may have an insidious progression, with serial declines in performance scores and weights. With continued therapy for more than 12 months, however, no cumulative DLTs have been recognized. A larger

experience with this combination will better characterize the full DLT spectrum.

Of patients who received at least one full cycle of combined imatinib plus docetaxel, 24% experienced a decline in entry-level PSA by 50% that maintained for 8 weeks. There are two prior phase II studies of weekly docetaxel therapy for comparison with the results from this phase I trial. Both these studies were in taxane-naïve AIPC with minimal or no prior chemotherapy, in contrast to our patient population (Table 1). Berry et al¹² treated 60 patients with weekly docetaxel at 36 mg/m² for 6 of 8 weeks. A 41% rate of PSA decline by 50% maintained for 4 weeks was observed, with a median duration of PSA response of 5 months and time to progression of 6.6 months (range, 3.2 to 18.2 months) for PSA responders. Beer et al¹³ treated 25 patients in a similar schedule and observed a 46% (95% CI, 25% to 67%) decline in PSA by 50% maintained for 4 weeks. The median time to PSA progression among responders was 20 weeks (range, 12 to 87 weeks). The median time to PSA response by 50% with weekly docetaxel alone is close to 30 days. In our study, the pattern and duration of responses with docetaxel and imatinib in combination appear qualitatively different from the historical single-agent data, with a prolonged median time to response (150 days), variable PSA fluctuations, and long periods of disease control in responding patients. Two of these responses are ongoing beyond 18 months. The median duration of PSA response of 8 months, and progression-free survival interval of 11 months for responders, appear superior to results obtained with single-agent docetaxel in populations with minimal prior exposure to chemotherapy.

As described earlier, one patient experienced an apparent reversal of docetaxel resistance with imatinib after previous disease progression on docetaxel was noted. This singular observation raises the possibility that signaling pathways that are inhibited by imatinib, such as those mediated by PDGFR, may play a role in docetaxel resistance. We speculate that a significant decline in PDGFR-expressing tumor burden in the bone marrow on combination therapy, but not single-agent therapy, infers successful targeting of PDGFR-expressing tumor in a preferential manner with combination therapy. If validated, expression profiling of PDGFR-negative tumors may offer insights into resistance to PDGFR-targeted therapy.

The significance of these several observations can only be estimated by a properly designed phase II trial, such as a randomized design that harmonizes eligibility and response outcomes and stratifies patients on entry for prognostic factors of importance.

We believe that the usefulness of combining the PDGFR inhibitor imatinib mesylate with docetaxel in prostate cancer is worthy of formal study. An ongoing randomized placebo-controlled phase II study of docetaxel and imatinib in AIPC with bone metastases in patients with no

prior taxane exposure, will evaluate differences in time to progression, as well as whether PDGFR expression in tumor in bone affects outcome. A crossover provision for the placebo arm will offer insights into the potential for imatinib to reverse docetaxel resistance.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for

drugs or devices used in a study if they are not being evaluated as part of the investigation. Owns stock (not including shares held through a public mutual fund): Peter F. Thall, Millenium Pharma. Acted as a consultant within the last 2 years: Isaiah J. Fidler, Novartis; Paul Mathew, Aventis, Novartis; Christopher Logothetis, Aventis, Novartis; Peter F. Thall, Orphan Medical, Novartis. Performed contract work within the last 2 years: Isaiah J. Fidler, Novartis. Received more than \$2,000 a year from a company for either of the last 2 years: Peter F. Thall, Orphan Medical, Novartis; Isaiah J. Fidler, Novartis; Paul Mathew, Aventis, Novartis.

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