A phase II trial of imatinib mesylate in patients with biochemical relapse of prostate cancer after definitive local therapy

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OBJECTIVE

To determine the biological effects of imatinib mesylate (STI-571, Gleevec®; Novartis Pharmaceuticals, Inc., East Hanover, NJ, USA), as measured by prostate-specific antigen (PSA) kinetics in men with biochemical relapse of prostate cancer after definitive local therapy.

PATIENTS AND METHODS

Men with prostate cancer, who had had definitive local therapy, with nonmetastatic recurrent disease as manifested by a rising PSA level, were enrolled on this phase II trial. Men received 400 mg of imatinib mesylate orally twice daily and continuously until disease progression or unacceptable toxicity. The PSA level was measured monthly.

RESULTS

In all, 20 men with biochemically relapsed prostate cancer were treated. The median pretreatment PSA level was 5.4 ng/mL. Of the 19 evaluable men, one achieved a ≥50% reduction in PSA level and two had decreases of <50%. For the 16 men in whom the on-treatment PSA doubling time (PSADT) could be calculated (those with increasing PSA level) the median PSADT did not increase significantly (5.8 vs 7.2 months, $P = 0.64$). Eleven of 20 men discontinued therapy due to toxicity and the trial was stopped early due to toxicity.

CONCLUSIONS

Based on the lack of PSA modulation and pronounced toxicities leading to early closure of this trial, further study of single-agent imatinib mesylate at this dose (400 mg twice daily) cannot be recommended in this patient population.

KEYWORDS

imatinib mesylate, prostate cancer, biochemical relapse

INTRODUCTION

About 230 110 new cases of prostate cancer are diagnosed annually in the USA [1]. Of men receiving definitive local therapy for prostate cancer, 20–60% (≈ 50 000 men per year) will develop recurrent disease [2] in which a rising PSA level is the only manifestation of treatment failure (biochemical relapse, BCR) [3]. Currently there is no standard of care for these men. Although androgen-deprivation therapy (ADT) is a therapeutic option, the short- and long-term side-effects (i.e. loss of libido, fatigue, muscle wasting, osteoporosis, anaemia) make this therapy less desirable for many patients and their physicians.

New and effective therapies are needed with low toxicity profiles for these asymptomatic patients. Testing the efficacy of novel therapeutics in men with BCR is difficult because: (i) there is great diversity in clinically relevant outcomes, such as time to metastases and time to prostate-cancer specific death; and (ii) the time to these clinically relevant endpoints is long. One potential intermediate endpoint is the PSA doubling time (PSADT). There are many retrospective data in men with BCR supporting the utility of PSADT in predicting metastatic disease risk and prostate cancer-specific survival [4–7]. Although the native PSADT after definitive local therapy predicts the time to metastases and prostate cancer-specific survival, alterations in PSADT due to treatment interventions have not yet been proven to alter clinical outcome. Similarly, while a ≥50% PSA decline has been considered a useful screen for the activity of cytotoxic agents used for treating hormone-refractory prostate cancer (HRPC) [8], this endpoint has not been validated in men with BCR. Nevertheless, a possible screening method for novel agents in men with BCR might be to determine which agents show potential biological effects (e.g. slowing of PSA rise, i.e. PSADT, or evidence of PSA declines). Modulation of PSA level by a novel agent might indicate biological activity that should be further investigated.

Imatinib mesylate (STI-571, Gleevec®; Novartis Pharmaceuticals Inc., East Hanover, NJ, USA), a phenylaminopyrimidine derivative, is an inhibitor of the receptor tyrosine kinase inhibitor BCR-Abl, c-kit and platelet-derived growth factor receptor (PDGF-R). PDGF is involved in autocrine stimulation of tumour cells, regulation of tumour stromal fibroblasts, and tumour angiogenesis [9]. PDGF-R has two subunits, α and β, which either homo- or heterodimerize upon binding of PDGF. PDGF-R was reported to be expressed on prostate cancer cells in several studies. Using immunohistochemistry (IHC), Ko *et al.* [10] showed that PDGF-R α and β were expressed in 88% of primary prostate tumours (hormone-sensitive, $n = 23$) and in 80% of bone marrow metastases (hormone-refractory, $n = 15$). Fudge *et al.* [11,12] similarly showed IHC expression of PDGF-R α in prostate adenocarcinomas and prostatic intraepithelial neoplasia, but not BPH specimens.

Previous trials of PDGF-R inhibitors showed only limited activity in metastatic HRPC. Ko

et al. [10] reported that 8% of 44 men with metastatic HRPC had a ≥50% PSA level decline in response to single-agent SU101 (Sugen, Inc., South San Francisco, CA, USA), an i.v. PDGF-R inhibitor with a short half-life. Similarly, Mathew *et al.* [13] reported that none of 28 men with metastatic HRPC had a ≥50% PSA decline during a 30-day lead-in phase of imatinib 600 mg daily alone, administered before the addition of chemotherapy.

As PDGF-R is expressed by prostate cancer cells and tumour vasculature, there is a biological rationale for targeting this particular signalling pathway for prostate cancer. Although the efficacy of the PDGF-R inhibitors in men with metastatic HRPC appeared limited, the men in these trials not only had more advanced disease, but were also heavily pre-treated. Potentially, the use of a biological agent such as imatinib in men with less advanced disease would be more effective. Thus, a prospective phase II trial in men with BCR after definitive local therapy was conducted. The primary endpoint for this trial was to determine the effects of imatinib on inducing declines in PSA level and modulating PSA kinetics.

PATIENTS AND METHODS

This was a single-arm phase II study conducted at the University of California, San Francisco (UCSF). Men with histologically confirmed adenocarcinoma of the prostate who had previous definitive local therapy with radical prostatectomy (RP), external beam radiotherapy, or brachytherapy were eligible. Disease progression after local therapy was defined as a rising PSA level based on three PSA determinations, each ≥2 weeks apart, and an absolute PSA value of ≥0.4 ng/mL. The men were required not to have metastatic disease, as shown by a negative bone scan and CT of the abdomen and pelvis within 6 weeks before initiating treatment. Adequate bone marrow, liver and renal function were required within 2 weeks of initiating treatment, including: absolute neutrophil count of ≥1500 cells/μL, haemoglobin of ≥8.0 g/dL, platelets ≥120 000 cells/m^3, serum creatinine level of ≤1.5 times the upper limit of normal, bilirubin ≤1.5 times the upper limit of normal, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of ≤1.5 times the upper limit of normal. A Karnofsky

Previous hormonal therapy (LHRH agonist and/or antiandrogen) for the treatment of progressive disease was not permitted, but previous adjuvant and/or neoadjuvant ADT was permitted if the ADT was ≤12 months in duration and was completed ≥12 months from the date of enrolment. The testosterone level at enrolment was required to be >250 ng/mL. Previous chemotherapy, ketoconazole, and PC-SPES (or other herbal preparations intended to lower testosterone) were not permitted. Concurrent use of finasteride or saw palmetto (*Serenoa repens*) was not allowed and men must have discontinued the drug for ≥4 weeks before study enrolment. No supplements, with the exception of conventional multivitamins, selenium, lycopene, and soy supplements, were permitted. Men receiving therapeutic anticoagulation with warfarin (coumadin) were excluded from the study because of the potential interaction with imatinib. All patients signed an informed consent form approved by the UCSF Institutional Review Board.

The men received imatinib 400 mg (all doses are expressed as orally twice daily) continuously, with one cycle consisting of 4-week intervals. This dose was selected on the basis of doses used in other diseases (chronic myelogenous leukaemia, gastrointestinal stromal tumour) that were felt to be safe with effective receptor inhibition. The men were evaluated at monthly intervals with laboratory and PSA measurements for the first 6 months, and every 3 months thereafter. Testosterone, dihydrotestosterone (DHT), androstenedione (DHEA), oestradiol and sex-hormone binding globulin (SHBG) levels were measured at the same time as PSA. Changes in hormone levels were expressed as a percentage change from baseline to make comparisons between men who had laboratory values measured at different facilities. After an interim analysis leading to early study closure due to excess toxicity, men who chose to continue on study had monthly laboratory and clinical assessments even if they had been treated for >6 months. Men had a baseline (pretreatment) bone scan and CT of the abdomen and pelvis that was repeated at the time of disease progression by PSA criteria (see above) or if clinically indicated. The criteria for PSA progression were based on PSA changes after the administration of imatinib for ≥3 months, so that men were not removed from the study

knowing *a priori* the impact of a biological agent such as imatinib on PSA levels, and the desire for an adequate time to follow the PSA trajectory. Disease progression and time to progression was defined by the PSA Consensus Criteria [8]. The PSADT, an estimate of the rate of change of PSA, was calculated before and during treatment as an additional measure of treatment effect (PSADT = natural log 2/slope of the rate of change of natural log PSA). The treatment continued until patients had evidence of disease progression by PSA Consensus Criteria, development of metastases, or experienced unacceptable toxicity.

The National Cancer Institute Cancer Clinical Trials Common Toxicity Criteria version 2.0 was used to assess toxicities. For all grade 2, 3 or 4 non-haematological toxicities, imatinib was held until resolution to ≤grade 1 and the drug dose was adjusted as follows: for the first occurrence of grade 2 non-haematological toxicities, the drug was resumed at the same dose (400 mg). If there was recurrence of the grade 2 toxicity, the drug was restarted at a reduced dose of 300 mg. If there was second recurrence of the grade 2 toxicity, the drug was discontinued but an option of remaining on the drug at a further reduced dose (200 mg) was permitted if the patient was responding. For the first occurrence of grade 3 or 4 non-hematological toxicity, imatinib was restarted at a lower dose of 300 mg. If there was a recurrence of the grade 3 or 4 toxicity, imatinib was restarted 200 mg. If there was a second recurrence of the grade 3 or 4 toxicity, imatinib was discontinued. Discontinuation of imatinib was recommended if there was interruption of treatment for ≥14 days to allow for recovery from toxicity.

No dose interruptions or reductions were undertaken for grade 1 or 2 haematological toxicities. For grade 3 or 4 haematological toxicities, excluding anaemia, imatinib was held until toxicity had resolved to ≤grade 1. If the toxicity resolved within 2 weeks of discontinuing the drug, drug was resumed at the same dose. If the grade 3 or 4 toxicity recurred or persisted for >2 weeks, the drug was held and resumed at a lower dose (300 mg) if the toxicity resolved to ≤grade 1. If there was another recurrence of grade 3 or 4 toxicity, imatinib was discontinued.

The primary endpoint for the present study

Characteristic	Median (range) or N (%)
Age, years	67.5 (54–85)
Primary local therapy	
RP	3 (15)
RT	6 (30)
RP and RT	11 (55)
Previous ADT with local therapy	6 (30)
Previous investigational therapy	4 (20)
Pretreatment PSA level, ng/mL	5.4 (0.5–13.3)
Gleason score	7 (5–9)
5	1 (5)
6	3 (15)
7	11 (55)
8	3 (15)
9	1 (5)
Unknown	1 (5)
Baseline testosterone level, ng/mL	434.5 (277–990)
Pretreatment PSADT, months	6.7 (2.9–38.5)

TABLE 1 The patients' characteristics (20 patients)

RT, radiation therapy (external-beam, brachytherapy).

observed with imatinib treatment. The sample size was determined using Gehan's two-stage design. Overall, if 15% of patients had PSA declines of ≥50%, this would be considered worthy of further study. If there were no PSA declines of ≥50% in the first 19 patients, no more patients would be enrolled (because the probability of observing at least one response if the expected probability of response is 15% is <5%). This sample size would result in a maximum 95% CI of length ± 17.9%. If at least one PSA decline of ≥50% occurred, accrual would continue for a total of 30 patients.

Descriptive statistics were calculated to characterize the patient group including the proportion responding with a 95% CI. The Wilcoxon-matched pairs test was used to compare the pretreatment and on-treatment PSADTs. For a safety evaluation, with 30 patients the study had 87% power to reject a null hypothesis of <5% probability of serious adverse events vs a 20% rate, with a level of significance of 0.061. Thus, if there were four or more grade 3 or 4 toxicities, the null hypothesis would be rejected due to lack of safety.

RESULTS

In all, 20 men with serological progression of prostate cancer were enrolled between April 2003 and October 2004. Table 1 lists the patient characteristics before treatment.

67.5 (54–85) years. The primary therapy included RP in three men, radiation in six, or RP followed by radiation therapy in 11. Six men (one who had a previous RP and five who had previous radiation therapy) had received previous neoadjuvant and/or adjuvant ADT. These men received a median (range) of 4 (3–12) months of ADT that had been discontinued for a median (range) of 58 (28–106) months before treatment with imatinib. Four men had received previous investigational treatments including APC8015 (Provenge®; Dendreon, Seattle, WA, USA), granulocyte-macrophage colony-stimulating factor (Leukine ®; Berlex, Seattle, WA, USA), bevacizumab (Avastin®; Genentech, South San Francisco, CA, USA), and rosiglitazone (Avandia®; GlaxoSmithKline, Philadelphia, PA, USA). The median (range) duration from the last investigational therapy before enrolling on the imatinib study was 11.43 (2–50.6) months. The median pretreatment PSA was 5.4 (0.50–13.30) ng/mL. Fifteen men (75%) had a Gleason score of ≥7. The median baseline testosterone level was 434.5 (277.0–990.0) ng/mL. The PSA values to calculate the pretreatment PSADT were not prospectively obtained before imatinib therapy. Pretreatment PSADT was calculated based on available pre-enrolment PSA values (see below). The median pretreatment PSADT for all men was 6.7 (2.9–38.5) months.

CLINICAL OUTCOMES

The median (range) treatment duration for all

men had >3 months of treatment; 19 men were evaluable for assessment of on-treatment PSA changes with a median follow-up of 12.6 months. One patient withdrew consent due to toxicity and did not have an on-treatment PSA sample drawn. Four men stopped protocol therapy before 3 months of therapy because of toxicity, while one stopped because of a rapid rise in PSA after 7 weeks of treatment. One of the 19 evaluable patients (5%) had a PSA decline of ≥50%. His pretreatment PSA was 6.0 ng/mL and the pretreatment PSADT was 11.4 months. By week 8 (at the end of 2 months of treatment), his PSA had declined to 0.1 ng/mL and by week 16 (at the end of 4 months of treatment), his PSA level was <0.1 ng/mL. However, he was removed from treatment due to the discovery of asymptomatic 'cotton-wool spots' (grade 2) on routine eye examination after 17 weeks of treatment.

Two other men had PSA declines of <50%; both declines (29% and 9.6%) were not sustained, occurring after 12 and 16 weeks of treatment, respectively. Both men eventually came off treatment for PSA progression, after 67 weeks and 53 weeks of treatment, respectively.

To determine the pretreatment PSADT, a median of six PSA values were used (range 3–17) and were collected over a median (range) of 11.2 (1.1–61.9) months. The median estimated pretreatment PSADT for all 20 men was 6.7 months, with a broad range of 2.9–38.5 months. Of the 19 evaluable men, three could not have an on-treatment PSADT calculated because they had declining PSA values. For the remaining 16 men for whom an on-treatment PSADT could be calculated, the median pretreatment and on-treatment PSADT was 5.8 vs 7.2 months, respectively ($P = 0.64$) (Table 2). Figure 1 shows the paired pretreatment and on-treatment PSADTs for each patient. There was no statistically significant difference in pretreatment and on-treatment PSADT among the 16 evaluable men, as well as among those who received >3 months of therapy. Overall, five of the 16 men for whom an on-treatment PSADT could be calculated had a >100% increase in their on-treatment PSADT compared with their pretreatment PSADT, with increases of 118%, 143%, 145%, 200% and 393%.

Upon discontinuation of imatinib and in the absence of further therapy, eight of the 19

compared with their last PSA value on-study, ranging from 11.1% to 44.8%. There were no declines of >50%.

The overall disposition of the men is outlined in Table 3. Of the 20 enrolled men, six developed progressive disease by PSA Consensus Criteria, with a median time to progression 3.56 (range, 1.75–14.43) months, and were removed from treatment. All six of these men had a follow-up bone scan and CT after stopping treatment. Four of five men had a positive bone scan at the time of PSA progression while the sixth was found to have enlarged perirectal nodes. Eleven men discontinued therapy due to toxicity (see below). Three men stopped protocol therapy before meeting the PSA progression criteria at 16, 31 and 40 weeks of treatment at the time of study closure, when an interim analysis revealed excess treatment toxicity.

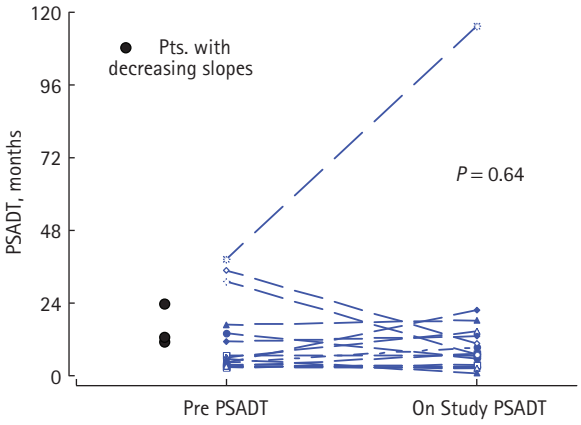

FIG. 1.
The paired pretreatment and on-treatment PSADTs.

Characteristic	Pretreatment	On-treatment
Pretreatment PSA, ng/mL		
Median (range)	5.1 (0.5–13.3)	
PSADT, months		
Median (range)	5.8 (2.9–38.5)	7.2 (2.8–115.5)
Mean	11.8	15.2

TABLE 2
The pretreatment and on-treatment PSA kinetics for the 16 evaluable patients

TOXICITY

Table 4 lists the observed toxicities. The most common haematological toxicities were grade 1 anaemia and grade 2 lymphopenia, with no clinically relevant consequences. The most common non-hematological toxicities were grade 1 periorbital oedema, fatigue and rash. Five men (25%) required dose reductions secondary to toxicity and 11 (55%) had toxicities leading to removal or withdrawal from the study.

Seven men developed grade 3 or 4 toxicities, five of which were attributable to imatinib. The first developed grade 4 neutropenia after 4 weeks of therapy and required a dose reduction to 300 mg. However, at 11 weeks, he developed grade 3 neutropenia and was removed from the study. The second developed a grade 3 rash and pruritus after 2 weeks of therapy and required a drug dose reduction to 300 mg. Subsequently, he developed multiple grade 2 side-effects (headache, nausea, malaise, fatigue, nausea) after a total of 5.5 weeks of treatment and withdrew consent. The third developed grade 3 diarrhoea after 14 weeks of treatment and withdrew consent. The fourth developed a grade 3 rash and grade 2 lower extremity oedema as well as grade 2 elevated AST, ALT and alkaline phosphatase after 3 weeks of treatment. Because of the severity of the rash, in addition to the development of extremity oedema and transaminitis, he was removed from study without attempting a dose reduction. The fifth developed grade 2 periorbital oedema, requiring dyazide after 1 week of treatment; after holding imatinib and restarting at the same dose, he developed grade 2 hypocalcaemia after 4 weeks of treatment. Imatinib was held and restarted at the same dose. Subsequently, after 7 weeks of treatment, he developed grade 2 conjunctivitis that was being treated with antibiotics. Imatinib was again held and restarted at the same dose. After 10 weeks of treatment, he developed grade 4 dyspnoea requiring diuretics and a dose reduction to 300 mg. At this reduced dose, he developed recurrent grade 2 conjunctivitis after a total of 12 weeks of therapy and was removed from treatment. Two men developed toxicities thought not to be related to imatinib, including a grade 4 large bowel obstruction and a grade 3 infection (perinephric abscess).

Six men had multiple grade 1 or 2 toxicities leading to removal from or withdrawal of consent from the study (Table 5). Two of the six had previously had grade 3 or 4 toxicities and had their dose reduced when they developed the grade 1 or 2 toxicities, leading to treatment discontinuation. The only man to have a ≥50% PSA decline (to <0.1 ng/mL) was removed from the study for development of asymptomatic, 'cotton-wool' spots (grade 2) discovered during a routine eye examination after 17 weeks of treatment. He had no history of hypertension, diabetes or collagen vascular disease. 2 months after imatinib was discontinued, a follow-up eye examination showed resolution of the cotton-wool spots and the toxicity was thus attributed to imatinib. His PSA levels after discontinuing imatinib remained low; his last PSA value, at 9 months after imatinib discontinuation, was 0.5 ng/mL.

TABLE 3 Patient disposition

Reason for coming off study	N (%)
Number of patients	20
Toxicity	11 (55)
PSA progression	5 (25)
Objective progression	1 (5)
Patient choice (at study closure)	2 (10)
Treating physician's discretion	1 (5)

EARLY STUDY CLOSURE

At the interim analysis after enrolment of the first 20 patients, the study met its efficacy endpoint (one of 19 patients with a ≥50% PSA level decline) and could continue to enrol patients with a target accrual goal of 30 patients. Five men developed grade 3 or 4 toxicities attributable to imatinib, indicating that the acceptable toxicity level of 5% could not be achieved. The number of men (11) who stopped therapy because of toxicity (ranging from grade 1 to 4) had exceeded the number

TABLE 4 Maximum grade of toxicity observed

Toxicity	Number of patients (%) Grade 1	Grade 2	Grade 3	Grade 4	Total
Haematological:					
Anaemia	16 (80)	0	0	0	16 (80)
Lymphopenia	1 (5)	12 (60)	1 (5)	0	14 (70)
Leukopenia	5 (25)	5 (25)	0	0	10 (50)
Neutropenia	4 (20)	1 (5)	0	1 (5)	6 (30)
Non-haematological:					
Periorbital oedema	14 (70)	2 (10)	0	0	16 (80)
Fatigue	7 (35)	5 (25)	0	0	12 (60)
Rash	8 (40)	1 (5)	2 (10)	0	11 (55)
Diarrhoea	4 (20)	2 (10)	2 (10)	0	8 (40)
Muscle cramps	6 (30)	0	0	0	6 (30)
Elevated ALT	4 (20)	1 (5)	1 (5)	0	6 (30)
Lower extremity oedema	4 (20)	1 (5)	0	0	5 (25)
Nausea	4 (20)	1 (5)	0	0	5 (25)
Flatulence	4 (20)	0	1 (5)	0	5 (25)
Elevated AST	3 (15)	2 (10)	0	0	5 (25)

TABLE 5 Toxicities leading to discontinuation of therapy

Patient	Treatment duration, weeks	Toxicity	Related to imatinib
2	11	Recurrent grade 3 neutropenia	Yes
3	5.5	Grade 3 rash, pruritus; grade 2 headache, nausea, malaise, fatigue	Yes
7	19	Grade 1 periorbital oedema, fatigue, arthritis, diarrhoea, visual light sensitivity	Yes
8	17	Recurrent grade 2 anorexia, taste alteration, weight loss	Yes
9	19.5	Grade 2 asymptomatic retinal cotton-wool spots	Yes
10	12	Grade 3 dyspnoea; grade 2 periorbital oedema, hypocalcaemia, recurrent conjunctivitis	Yes
11	14	Grade 3 diarrhoea	Yes
12	23	Grade 3 diarrhoea; grade 4 large bowel obstruction	No
15	7	Grade 2 airway oedema	Yes
16	7	Grade 3 infection	No
20	3	Grade 3 rash; grade 3 transaminitis, peripheral oedema	Yes

(six) who had stopped therapy for disease progression. Therefore, the decision was made to close the study early to further accrual. Men still receiving therapy were given the option of continuing the study treatment or withdrawing consent. Of the four men who were on study at the time, two chose to continue on study, and two withdrew consent.

HORMONAL CHANGES

To ensure that an effect of imatinib on PSA

hormone levels, testosterone, DHT, DHEA, oestradiol, and SHBG levels were measured. There was no evidence of changes in the testosterone, DHT, DHEA, or oestradiol levels over time, although SHBG levels tended to rise slightly (data not shown). For the patient with a dramatic PSA decline from 6.0 ng/mL to <0.1 ng/mL, his testosterone initially declined by 43% (404 ng/mL to 231 ng/mL) and subsequently rose to 651 ng/mL while on treatment. His DHT levels fell from above normal limits to below normal limits (maximum decline of 83%) and subsequently

His PSA remained undetectable throughout treatment despite these androgen level fluctuations.

DISCUSSION

There is no standard of care for men with BCR prostate cancer. While ADT is commonly used, many patients and physicians seek to delay its use. Imatinib is a reasonable agent to test in this setting, given the presence of PDGF-R on prostate cancer cells. Unfortunately, for men with BCR prostate cancer, single-agent imatinib had little effect, as measured by PSA declines and changes in PSADT. Only three of the 19 evaluable patients (16%) had a PSA decline and only one (5%) had a decline of ≥50%. The median PSADT was not significantly prolonged (5.8 vs 7.2 months, $P = 0.64$) although five of the 16 evaluable patients had a ≥100% increase in PSADT. More significantly, the leading cause of treatment discontinuation was toxicity (11 men), not progressive disease (six men). While only 25% of patients had a grade 3 or 4 toxicity attributable to imatinib, many of the milder toxicities had the potential to compromise quality of life in this normally asymptomatic group of patients, as shown by the number who discontinued therapy due to such toxicities. Based on the lack of significant efficacy as measured by changes in PSA, together with pronounced toxicities leading to early closure of this trial, further study of single-agent imatinib at this dose (400 mg) cannot be recommended in such patients. Notably, imatinib did not appreciably alter hormonal levels consistently, and the PSA declines that occurred did not appear to be mediated by androgen deprivation.

The present findings are similar to those reported by Rao *et al.* [14] and Bajaj *et al.* [15]. Using a similar study design, Rao *et al.* conducted a phase II study of single-agent imatinib in 21 men with BCR prostate cancer. Patients received a similar dose of imatinib at 400 mg twice daily for 24 weeks. None of the 16 evaluable men had any PSA decline and seven had PSA progression. Toxicities were also encountered, with seven men (33%) requiring a dose reduction and six (29%) unable to complete the 24 weeks of therapy because of toxicity. The toxicities were similar to those in the present report, including rash, neutropenia, diarrhoea, shortness of breath, and chest pain. IHC staining of primary

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