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ORIGINAL REPORT

Randomized Phase II Study of Two Doses of Gefitinib in Hormone-Refractory Prostate Cancer: A Trial of the National Cancer Institute of Canada-Clinical Trials Group

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ABSTRACT

Purpose

Overexpression of the epidermal growth factor receptor has been demonstrated in advanced prostate cancer and is associated with a poor outcome. A multi-institutional, randomized, phase II study was undertaken by the National Cancer Institute of Canada-Clinical Trials Group to evaluate the efficacy and toxicity of two doses of oral gefitinib in patients with minimally symptomatic, hormone-refractory prostate cancer (HRPC).

Patients and Methods

Between July and November 2001, 40 patients with HRPC and increasing prostate-specific antigen (PSA) or progression in measurable disease who had not received prior chemotherapy were randomly assigned to 250 mg (n = 19) or 500 mg (n = 21) oral gefitinib daily continuously. The primary end points were PSA response rate and objective measurable response. Functional Assessment of Cancer Therapy Prostate Cancer Subscale (FACT-P) quality-of-life questionnaires were completed at baseline and during treatment.

Results

None of the patients demonstrated a PSA or objective measurable response. Five (14.3%) of 35 assessable patients had stable PSA (one patient at 250 mg and four patients at 500 mg), and five patients (14.3%) had a best response of stable disease (duration, 2.5 to 16.8 months). No significant effect on the rate of increase in PSA was seen. The most common drug-related nonhematologic toxicities observed were grade 1 to 2 diarrhea (250 mg, 65%; 500 mg, 56%), fatigue (250 mg, 29%; 500 mg, 33%), and grade 1 to 2 skin rash (250 mg, 24%; 500 mg, 39%). FACT-P scores decreased during treatment, indicating worsening of symptoms compared with baseline.

Conclusion

Gefitinib did not result in any responses in PSA or objective measurable disease at either dose level. Gefitinib has minimal single-agent activity in HRPC.

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INTRODUCTION

Prostate cancer is the most common male cancer and the second leading cause of cancer death in men, accounting for an estimated 33,000 deaths in North America annually.[1,2] Patients with advanced or metastatic disease are incurable. Androgen ablation is standard first-line therapy for these patients, and although 80% will initially respond to androgen withdrawal, the median duration of response is approximately 18 months. Once a patient develops metastatic hormone-resistant disease, the median survival is 9 to 18 months. Subsequent therapeutic options are limited, and treatment

goals focus on palliation of symptoms such as fatigue, bone pain, and weight loss. Although chemotherapy has been shown to improve quality of life and pain control, no improvement in survival has yet been demonstrated.[3] With the earlier use of androgen ablation and frequent use of prostate-specific antigen (PSA) for monitoring, patients with hormone-refractory prostate cancer (HRPC) are now more commonly identified at an earlier stage by an increasing PSA rather than by new or worsening symptoms as in the past. These patients are often asymptomatic when initially seen, although progression to symptomatic disease usually occurs within 6 to 12 months. Because conventional chemotherapy has not been shown to benefit these patients, they are an appropriate group in which to test new approaches to therapy. In addition, these clinically stable patients can tolerate the 2- to 3-week time period often required to achieve therapeutic steady-state and allow for an assessment of any potential cytostatic activity associated with many of the novel oral agents currently under investigation.

In vitro proliferation of prostate epithelial cells cannot be induced by androgens alone but requires costimulation by a number of growth factors, including epidermal growth factor (EGF).[4,5] EGF binds to its receptor, inducing conformational changes within the receptor and increasing the activity of associated tyrosine kinases. This results in increased biologic activity, including cell proliferation and/or differentiation. Abnormal EGF receptor (EGFR) expression, either mutation or overexpression, has been demonstrated in many malignancies including prostate cancer.[6-10] EGFR is an ideal molecular target for inhibition because it is overexpressed in many tumor cells, yet it is strictly controlled in normal cells. Several inhibitors of the EGFR are in clinical testing. The two major categories of inhibitors are antibodies to the external epitope and small molecule inhibitors of the receptor tyrosine kinase.

Gefitinib (4-[3-chloro-4-fluorophenylamino]-7-methoxy-6-[3-{4-morpholinyl}propoxy]quinazoline, Iressa, ZD1839; AstraZeneca Pharmaceuticals, Mississauga, Canada) is an orally administered quinazoline-based molecule that inhibits EGFR tyrosine kinase. In preclinical models and early clinical studies, inhibition of EGFR has resulted in antitumor activity.[11] Growth inhibition and tumor regression has been seen in human xenograft models in lung, prostate, breast, and colorectal cancers.[12-15]

More than 250 patients with advanced solid tumor, including prostate cancer, were enrolled onto phase I studies of gefitinib[16-21] The maximum-tolerated dose was determined to be 700 to 1,000 mg/d, with diarrhea as the dose-limiting toxicity. Serial skin biopsies have confirmed inhibition of EGFR tyrosine kinase in cancer patients.[16] Responses and stable disease were observed in some patients, particularly in non–small-cell lung cancer and head and neck cancer, with some activity reported against prostate cancer. Once-daily oral doses of 250 mg and 500 mg, which are below the maximum-tolerated dose but have plasma concentrations above those required to maximally inhibit EGFR, were selected for further clinical investigation.[21] The US Food and Drug Administration has approved gefitinib (ZD1893) as monotherapy treatment for patients with locally advanced or metastatic non–small-cell lung cancer after failure of both platinum-based and docetaxel chemotherapies on the basis of phase II studies showing response in refractory patients.[22-26] In other phase II studies of gefitinib, activity has been seen in head and neck cancer, although results in renal and bladder cancer have been disappointing.[27,28]

Given the high expression of EGFR in prostate cancer, the preclinical activity and responses in phase I, and the urgent need for new approaches for HRPC, a phase II trial of two doses of oral gefitinib was initiated by the National Cancer Institute of Canada-Clinical Trials Group.

PATIENTS AND METHODS

Patient Eligibility

Patients with histologic or cytologic evidence of adenocarcinoma of the prostate, increasing PSA $\geq$ 20 ng/mL, or increasing measurable disease while receiving androgen-ablative therapy were eligible. Androgen-ablative therapy was defined as surgical or medical castration, with testosterone level $\leq$ 50 ng/mL. Patients were required to have discontinued peripheral antiandrogen therapy for $\geq$ 4 weeks ($\geq$ 6 weeks for bicalutamide) before study entry, but luteinizing hormone-releasing hormone agonist was continued; if discontinued, it was restarted. Increasing PSA was defined as $\geq$ 25% increase in reference value of PSA (absolute value of increase, $\geq$ 5 ng/mL) a minimum of 1 week from the reference value and confirmed by a second increase in PSA at least 1 week later. To be considered measurable, a lesion must have measured at least 20 mm in one dimension with conventional techniques (physical examination, computed tomography, x-ray, or magnetic resonance imaging) or at least 10 mm with spiral computed tomography according to Response Evaluation Criteria in Solid Tumors.[29] An assessment of EGFR expression was not mandated initially but would have been performed if gefitinib demonstrated sufficient activity to proceed to the second stage of the study.

The institutional review boards at all participating sites approved the study protocol, and written informed consent was obtained before study. Other eligibility criteria included Eastern Cooperative Oncology Group performance status of 0 or 1, no prior chemotherapy, and no prior investigational agents. Radiation was permitted if $\geq$ 4 weeks had elapsed since treatment, and corticosteroids were permitted provided that no increase in dose was planned or had occurred within 4 weeks before randomization. Patients who required large amounts of narcotic therapy to control pain (eg, morphine equivalent dose of $>$ 60 mg/d) were excluded. If capable, patients must have been willing to complete quality-of-life assessments (Functional Assessment of Cancer Therapy Prostate Cancer Subscale [FACT-P]) in either English or French.[30]

Requirements for organ function were absolute granulocytes $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, serum creatinine and

bilirubin ≤ 2 × upper normal limits, and AST and ALT ≤ 2.5 × upper normal limits (≤ 5 × upper normal limit if liver metastases were present). Patients were excluded if they had any prior malignancy within the last 5 years, were receiving ketoconazole, or had any other serious medical condition or illness that would not permit the patient to be managed according to the protocol.

Study Design and Treatment

This was a multi-institutional study conducted by the National Cancer Institute of Canada-Clinical Trials Group at six participating centers (Princess Margaret Hospital; Toronto-Sunnybrook Regional Cancer Centre; London Regional Cancer Centre; McGill-Jewish General Hospital; Vancouver Prostate Centre; and Tom Baker Cancer Centre, Calgary). AstraZeneca Pharamaceuticals supplied gefitinib and provided some financial support for this study. Patients were randomly assigned to either 250 mg or 500 mg of gefitinib taken orally on a daily basis for a 28-day cycle. Hematology was examined weekly for two cycles and then on days 1 and 15 of subsequent cycles. Biochemistry, including PSA, was evaluated on day 1 of each cycle. Imaging of measurable disease was repeated on day 1 of every second cycle. Toxicity was assessed continuously and graded using the National Cancer Institute Common Toxicity Criteria version 2.0. Patients completed the quality-of-life questionnaire (FACT-P) on day 1 of each cycle.

Therapy was continued until treatment failure, unacceptable toxicity, intercurrent illness interfering with protocol treatment and/or assessment, patient request, or investigator discretion. Any patient who experienced grade 4 toxicity attributable to therapy was withdrawn from study. For patients with grade 3 toxicity or grade 2 renal or ocular toxicity, treatment was discontinued until toxicity resolved to ≤ grade 1. All patients, regardless of whether they had initially received 250 mg or 500 mg per day, were then rechallenged at 250 mg per day. If toxicity returned, they were removed from the study.

Response Assessment

All patients who received any gefitinib were assessable for toxicity. All patients who received at least one cycle of therapy or had objective progression or treatment failure in cycle 1 were considered assessable for response. Treatment failure was defined as new or worsening disease symptoms requiring change in management, a decrease in Eastern Cooperative Oncology Group performance status by two levels, new or objective progression in measurable disease, or a 25% increase over the baseline or nadir PSA value (whichever was lower), with an increase of at least 5 ng/mL, that is confirmed by a second measurement (a modification to Bubley et al).[31] PSA response was defined as a 50% decrease in PSA from baseline confirmed by a second PSA value ≥ 4 weeks later. Objective measurable response was evaluated using Response Evaluation Criteria in Solid Tumors criteria. Stable disease was defined as not meeting the criteria for complete response, partial response, or progressive disease.

Statistical Considerations

The primary end point of this study was response as determined by PSA and/or measurable disease (if present). A two-stage design based on both response and progression was used to allow for early closure if the drug was inactive.[32] The first stage was designed to accrue 15 patients in each arm. If two or fewer patients responded and there were nine or more early failures (within two cycles), the arm would be closed, and the regimen would be considered inactive. If these criteria were not fulfilled, an additional 15 patients would be accrued to that arm for a final set of 30 assessable patients per arm.

In addition to the planned analyses, an exploratory analysis was performed to determine doubling times of patient PSA levels before and during treatment with gefitinib. To be assessable for PSA doubling time, a minimum of three PSA levels (minimum of 5 days to a maximum of 5 months) were required before entry onto study. PSA values before and on study were plotted, linear regression analysis was performed, and a best-fit curve was generated for each graph before and during gefitinib. From the slope of the best fit curves, PSA doubling times were calculated using the following formula: doubling time = $\ln^2/b$. The percentage change in PSA doubling time on study was compared with PSA doubling time before study for each patient.

RESULTS

Patient Characteristics

The first patient was randomized in July 2001. In November 2001, after 40 patients had been enrolled, accrual was held pending assessment of response of the first cohort. When the criteria for closure were met at both dose levels, the study was then permanently closed. Five patients were not assessable; one patient was not treated, and four patients were deemed ineligible (two patients had prior chemotherapy with estramustine, one patient had a decreasing PSA when starting treatment, and one patient first started a luteinizing hormone-releasing hormone agonist just before study entry). Table 1 lists the demographics and clinical characteristics of the 35 assessable patients.

Seventeen and 18 assessable patients were randomly assigned to 250 mg and 500 mg of daily gefitinib, respectively. The median number of cycles administered was two (range, one to five cycles on 250 mg; and one to six cycles on 500 mg). All patients receiving 250 mg and 72% of patients on 500 mg of gefitinib received ≥ 90% of the planned dose. Two patients on 250 mg were taken off study because of toxicity (nausea and diarrhea; and fatigue and blurred vision), and two patients on 500 mg required a dose reduction because of rash, stomatitis, and edema. The most common toxicity was grade 1 to 2 diarrhea (65% on 250 mg and 56% on 500 mg), followed by fatigue (29% on 250 mg and 33% on 500 mg). Table 2 lists the drug-related adverse events that occurred in more than 10% of patients in either dose group.

Response to Treatment

In 35 assessable patients, there were no PSA responses seen; five patients had stable disease for 2 months or greater, 23 had progression within two cycles, and seven did not have sufficient values performed to define a response. Of 21 patients with measurable disease, there were no responses seen. In patients with nonprogression, the duration of disease stability ranged from 2.5 to 16.8 months. Twenty-six patients (74%) had sufficient prestudy and on-study PSA

Table 1. Baseline Patient Characteristics

Characteristic	Gefitinib Dose (N = 35) 250 mg/d (n = 17) No. of Patients	%	500 mg/d (n = 18) No. of Patients	%
Age, years				
Median	70		74	
Range	56-83		60-86	
ECOG performance status				
0	10	58.8	7	38.9
1	7	41.2	11	61.1
Baseline PSA				
Median	93		129	
Range	13-882		28-421	
Prior therapy				
Adjuvant hormone therapy	10	58.8	13	72.2
Hormones for metastatic disease	15	88.2	8	44.4
Radiotherapy	12	70.6	9	50.0
Other therapy	1	5.9	1	5.6
Measurable disease	11	64.7	10	55.6
Sites of disease				
PSA elevated only	0	0	1	5.6
Bone	12	70.6	15	83.3
Liver	0	0	1	5.6
Lung	1	5.9	0	0
Lymph nodes	10	58.8	12	66.7
Locoregional	3	17.7	0	0
No. of sites of disease				
No lesions	0	0	1	5.6
1	10	58.8	7	38.9
2	4	23.5	9	50.0
3	3	17.7	1	5.6

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

values to be eligible for an analysis of PSA doubling times. The median PSA doubling time was 71 days (range, 23 to 315 days) before study entry and 68 days (range, 22 to 315 days) while on study. Fifteen patients (58%) exhibited an increase in their PSA doubling time while on study, whereas 11 patients (42%) exhibited a decrease (Fig 1). There were eight patients who exhibited a greater than 50% increase in PSA doubling time. There was no apparent difference between patients receiving 250 mg or 500 mg of gefitinib.

FACT-P quality-of-life questionnaires were completed by 33 patients at baseline (94.3%), and conclusions are limited because of small sample size. The compliance rates were 71% (25 of 35 evaluable patients) and 63% (17 of 27 evaluable patients) at the beginning of cycles 2 and 3 during treatment, and 32% (10 of 31 evaluable patients) at the first 4-week assessment after off treatment. Little difference was seen between arms. In most cases, patient scores decreased during treatment, indicating worsening of symptoms compared with baseline scores.

Table 2. Drug-Related Adverse Events

Toxicity	Range of CTC Grade	Gefitinib Dose 250 mg/d (n = 17) No. of Patients	%	500 mg/d (n = 18) No. of Patients	%
Fatigue	1-3	5	29	6	33
Anorexia	1-2	4	24	3	17
Diarrhea	1-2	11	65	10	56
Nausea	1-2	5	29	3	17
Stomatitis	1-2	1	6	2	11
Taste disturbance	1-2	1	6	4	22
Vomiting	2	2	12	0	0
Alopecia	1	2	12	0	0
Dry skin	1	2	12	6	33
Rash/desquamation	1-2	4	24	7	39
Bruising	1	0	0	2	11

NOTE. Adverse events were not observed at CTC grades higher than those presented. Only events that occurred in more than 10% of patients in either dose group are reported.
Abbreviation: CTC, Common Toxicity Criteria.

DISCUSSION

Overexpression of EGFR in prostate cancer cells has led to development of novel therapeutic approaches targeting EGFR and its signal transduction cascade. Such approaches may include monoclonal antibodies directed against the extracellular ligand–binding domain of the receptor, antisense oligonucleotides directed against the expression of EGFR ligands or the receptor itself, low molecular weight inhibitors of the receptor tyrosine kinase activity, or low molecular weight compounds directed against the downstream components of the signal transduction pathway such as ras.[4] In addition to gefitinib, clinical investigations are underway to assess the activity of cetuximab, a

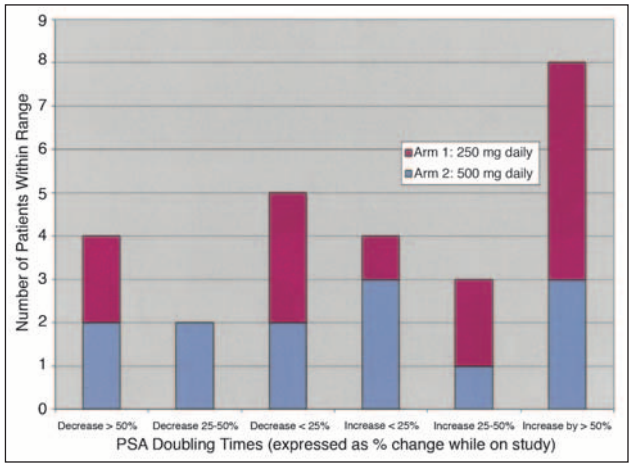

Fig 1. The effect of gefitinib on prostate-specific antigen (PSA) bdoubling times (n = 26).

monoclonal antibody against the external ligand-binding domain of EGFR, in patients with HRPC.

Our study did not demonstrate any activity for gefitinib as a monotherapy in HRPC at either 250 mg or 500 mg daily using conventional response criteria. An analysis of PSA doubling time did not show any significant effects on the rate of increase in PSA at either dose level. Another study of gefitinib (500 mg/d) in a similar patient population was recently presented in abstract form and similarly showed minimal activity.[33]

The results of this study were disappointing. It is improbable that the negative results seen were a result of poor compliance with therapy because these men were highly motivated to take their medications, and the toxicity seen was that expected. The effects were comparable at both dose levels, and there is no evidence from any tumor type that a higher dose than what was used in this study has a greater benefit. We did not biopsy the tumors before study entry to phenotype the tumors. This is difficult to do in patients with limited-volume advanced prostate cancer, and studies in other tumors where EGFR inhibitors have activity have not shown a clear correlation between EGFR expression and response.

The EGF signaling pathway remains an attractive target for cancer therapy. We need to understand more about interactions with other cell growth and signaling pathways and how to define when EGFR is a critical component of cancer proliferation. It is clear that a single targeted approach of inhibition of the EGFR pathway is inadequate to control tumor growth in HRPC, despite the frequent overexpression of EGFR that has been reported. Further assessment of EGFR inhibitors in prostate cancer need to focus on earlier stages of the disease or the use of EGFR inhibitors as a component of a multimodal strategy in combination with other targeted agents.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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