original contribution

Single-Agent Gefitinib in Patients with Untreated Advanced Non–Small-Cell Lung Cancer and Poor Performance Status: A Minnie Pearl Cancer Research Network Phase II Trial

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Abstract

BACKGROUND: Patients with advanced non–small-cell lung cancer (NSCLC) and poor performance status (PS) are often excluded from trials. Gefitinib is a safe oral agent that may benefit these patients. PATIENTS AND METHODS: Seventy-two patients with poor PS and advanced NSCLC were enrolled onto this study of gefitinib 250 mg per day given orally until disease progression, with evaluation at 8 weeks. Eligible patients had no previous chemotherapy, an Eastern Cooperative Oncology Group PS of 2/3, and stage IIIB/IV NSCLC. Quality of life (QOL) and symptom response (SR) scores were calculated using the Functional Assessment of Cancer–Lung questionnaire. Patient characteristics included a median age of 75 years; PS of 2/3; and bronchoalveolar (n = 3), adenocarcinoma (n = 29), squamous cell (n = 21), large-cell (n = 11), and unspecified histology (n = 6). Mean treatment duration was 4 months (range, 3 days to 18 months), and median duration of follow-up was 12 months. Grade 3/4 toxicities included rash and diarrhea. RESULTS: Among 70 patients assessed for response, there were 3 partial responses (4%), 32 patients with stable disease (46%), and 18 with progressive disease (26%). Median progression-free survival (PFS) and overall survival (OS) were 3.7 months and 6.3 months, respectively. Six-month and 1-year PFS and OS rates were 35% and 21% and 50% and 24%, respectively. Eighty-two percent and 48% of patients reported improvements or no change in QOL and SR, respectively. CONCLUSION: Gefitinib demonstrates modest efficacy and is well tolerated as initial therapy in advanced NSCLC for patients with poor PS.

Clinical Lung Cancer, Vol. 7, No. 2, 127-132, 2005

Key words: First-line treatment, Multicenter trial, Quality of life, Stage IIIB/IV disease

Introduction

Combination chemotherapy is recommended as first-line treatment for patients with advanced non–small-cell lung cancer (NSCLC) and good performance status (PS).[1] Randomized studies have confirmed that combination chemotherapy improves overall survival, symptoms of advanced disease, and quality of life (QOL) compared with best supportive care alone.[2-4] However, in patients with poor PS (Eastern Cooperative Oncology Group [ECOG] ≥ 2), combination chemotherapy may result in substantial toxicity.

Gefitinib is an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) approved by the US Food and Drug Administration (FDA) as single-agent therapy for patients with advanced NSCLC who have progressive disease after platinum agent–based and docetaxel chemotherapies. In 2 large phase II monotherapy studies in patients with advanced NSCLC who

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Submitted: Jun 6, 2005; Revised: Aug 1, 2005; Accepted: Aug 9, 2005

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Table 1 Visit Response Score

Score	Change from Baseline	Visit Response
Functional Assessment of Cancer—Lung	≥ +6	Worsened
	≤ −6	Improved
	Otherwise	No change
Lung Cancer Scale	≥ +2	Worsened
	≤ −2	Improved
	Otherwise	No change

Table 2 Quality of Life and Symptom Response Best Overall Response Scoring

Best Overall Response Score	Criteria
Improved	Two visit responses of "improved" a minimum of 28 days apart with no interim visit response of "worsened."
No Change	Does not qualify for overall score response of "improved"; 2 visit responses of "no change" or "improved" a minimum of 28 days apart with no interim visit response of "worsened."
Worsened	Does not qualify for overall score response of "improved" or "no change"; 2 consecutive visit responses of "worsened."
Other	Does not qualify for any of the listed score responses.

had received previous chemotherapy, gefitinib was associated with symptom improvement and objective tumor responses.[5,6] Adverse events in these trials were minimal and generally limited to grade 1/2 rash and diarrhea. Gefitinib's excellent safety profile and proven activity in refractory NSCLC make it an ideal agent to study in the first-line setting in patients with poor PS who are not candidates for combination chemotherapy.

We conducted a phase II trial of gefitinib in patients with poor PS and untreated advanced NSCLC based on established antitumor activity with gefitinib and limited systemic toxicity. The dose and daily schedule were derived from randomized studies and consistent with FDA approval. The results of the phase II trial are reported here.

Patients and Methods

Patients

This multicenter phase II trial was conducted in the Minnie Pearl Cancer Research Network, a community-based clinical trials group (see Appendix A). Eligibilty criteria included no previous chemotherapy or biologic therapy for advanced NSCLC; ECOG PS of 2/3; measurable disease; absolute neutrophil count ≥ 1500 cells/mL, platelet counts ≥ 100,000 cells/μL, hemoglobin ≥ 8.0 g/dL, normal liver function (bilirubin < 1.5 mg/dL and serum aspartate aminotransferase < 2 times the upper limit of normal); and signed informed consent. Exclusion criteria included parenchymal brain metastases, with the exception of patients with brain metastases previously treated with definitive resection and/or radiation therapy with no evidence of residual disease on imaging. The trial was approved by the institutional review boards at respective participating centers.

Dose and Treatment Schedule

Gefitinib was supplied by AstraZeneca Pharmaceuticals in 250-mg tablets. Patients received 4-week (28-day) supplies of gefitinib and were instructed to take 250 mg orally each morning. No routine premedications were required. Crushing tablets was not permitted. For patients unable to swallow whole tablets, gefitinib could be dissolved in water. Four weeks of therapy was considered 1 cycle of treatment. There were no dose reductions; however, treating physicians could hold gefitinib ≤ 14 days in the event of grade 3/4 toxicity. After toxicity resolved to grade ≤ 1, gefitinib was restarted at the previous dose of 250 mg per day. Gefitinib was discontinued only for disease progression or if unacceptable drug-related adverse events occurred. Because of potential drug interactions, concomitant use of CYP3A4 inducers (phenytoin, carbamazepine, rifampicin, phenobarbital, or St. John's Wort) was not allowed.

Outcomes Measured

The primary endpoint of the trial was to assess the overall response rate (ORR, partial plus complete response proportion) associated with gefitinib in patients with advanced NSCLC. Response was assessed according to bidimensional measurements (World Health Organization Response Evaluation Criteria), and toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Assessment of tumor size took place at the end of every two 4-week cycles. Patients with stable disease or better response received further treatment until disease progression or unacceptable toxicity. Patients were monitored with history, physical examination, PS, complete blood count, and comprehensive metabolic profiles every 4 weeks. Progression-free survival (PFS) was defined as the time from start of therapy to disease progression or last follow-up date, and overall survival (OS) was defined as the time from start of therapy to death or last follow-up date.

Quality of life was evaluated at baseline and every 4 weeks using version 3 of the Functional Assessment of Cancer—Lung (FACT-L) questionnaire.[7] This questionnaire uses a 5-point scale and addresses physical, functional, social, and emotional well-being, as well as lung cancer symptoms and concerns and relationship with the health care provider (not at all = 0, a little bit = 1, somewhat = 2, quite a bit = 3, and very much = 4). In addition, symptomatic response (SR) to treatment was evaluated at baseline and every week using the Lung Cancer Scale (LCS, subscale of FACT-L) diary. At a given visit, the criteria listed in Table 1 were used to assign a visit response score. At the conclusion of the trial, the criteria listed in Table 2 were used for each score, based on the individual visit responses, to assign a best overall response score. A best response for the FACT-L scores was calculated based on the absolute change from baseline.

Quality of life and SR score "improvement rates" were calculated as the percentage of all analyzed patients with a best over-

Table 3 Patient Characteristics

Characteristic	Number of Patients (%)
Median Age, Years (Range)	75 (55-88)
Sex	
Female	29 (41)
Male	41 (59)
Performance Status	
2	58 (83)
3	12 (17)
Histologic Subtype	
Adenocarcinoma	29 (41)
Squamous cell	21 (30)
Large cell	11 (16)
Bronchoalveolar	3 (4)
Unspecified	6 (9)
History of Smoking	
Yes	54 (96)*
No	2 (4)
History of Radiation Therapy	
Yes	12 (17)
No	58 (83)
History of Cerebral Metastases at Enrollment	
Yes	7 (10)
No	63 (90)

*Smoking histories not available on all patients.

all response score of "improved." A score "control rate" was calculated as the percentage of all analyzed patients with a best overall response score of "improved" or "no change." A "score worsened" rate was calculated as the percentage of all analyzed patients with a best overall response score of "worsened." Demographic data and summary statistics describing the study population (eg, ranges and medians of age, description of baseline PS, tabulation of tumors, and histologies) were measured. Safety data, which included laboratory parameters and adverse events, were tabulated for all patients.

With standard chemotherapy programs, response rates are approximately 10%-20%, with median survival of 3-5 months in patients with a PS of 2. It was hypothesized that the outcome of the treated patient group in this trial would be inferior to these reported statistics, because patients with a PS of 3 were included. The null hypothesis for this trial was that the overall response rate would be 5%. Therefore, an objective response rate ≥ 15%, QOL or symptom improvement rate of > 25%, or median survival ≥ 5 months would be study results that would merit further investigation of single-agent gefitinib in this patient population. The α level of the trial design was 0.05 and the power was 0.8.

Table 4 Patient Outcome (N = 70)

Response	Number of Patients (%)
Complete Response	0
Partial Response	3 (4)
Stable Disease	32 (46)
Progressive Disease	18 (26)
Unevaluable*	17 (24)

*Patients included in the response analysis who were unevaluable because of intercurrent illness (n = 2); patient compliance/request (n = 3); physician decision (n = 1); death (n = 4); rapid tumor progression (n = 2); and poor subjective response (n = 5).

Results

Patient Characteristics

From March 2003 to March 2004, 72 patients were enrolled on study. Two patients were ineligible because of a PS of 1. Baseline characteristics for all eligible patients are described in Table 3. The median age was 75 years (range, 55-88 years). Twenty-nine patients (41%) had adenocarcinoma histology; the others were of squamous (30%), large cell (16%), bronchoalveolar (4%), or unspecified subtype (9%). Fifty-eight patients (83%) had a PS of 2 and 12 patients (17%) had a PS of 3. The mean treatment duration was 4 months (range, 3 days to 18 months), and median duration of follow-up was 12 months (range, 6-18 months).

Response and Survival

Seventy patients were enrolled on study and treated with gefitinib. Seventeen patients did not complete ≥ 8 weeks (2 cycles) of treatment or undergo restaging studies (because of intercurrent illness, n = 2; patient compliance/request, n = 3; physician decision, n = 1; death, n = 4; rapid tumor progression, n = 2; or poor subjective response, n = 5) and were deemed unevaluable. However, all 70 patients are included in the response analysis (Table 4). Three patients (4%; 95% CI, 1%-11%) exhibited a partial response (PR) with response durations of 32, 45, and 51 weeks, respectively; 2 of these patients remain on study. The 3 responding patients included 2 women and 1 man, aged 66, 73,

Figure 1 Progression-Free Survival with Gefitinib in Patients with Advanced NSCLC and Poor Performance Status

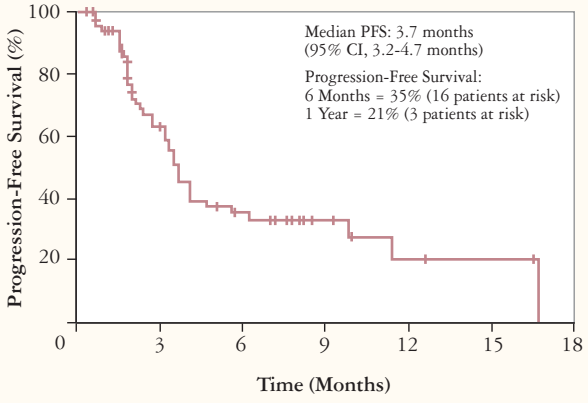
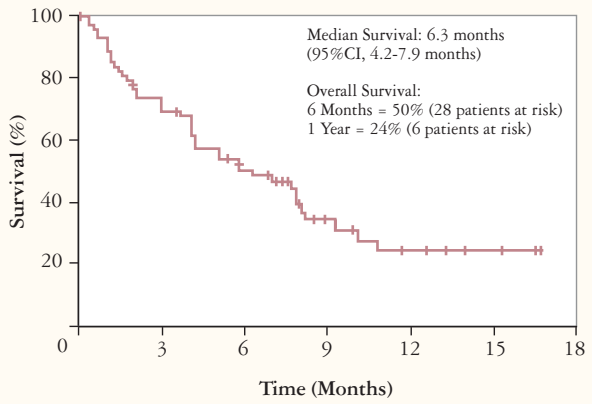


Figure 2 Overall Survival with Gefitinib in Patients with Advanced NSCLC and Poor Performance Status



and 83 years, with tumor histologies of adenocarcinoma (n = 2) and large cell (n = 2) and histories of smoking in all cases. Thirty-two patients (46%; 95% CI, 35%-58%) had stable disease (SD), and 18 patients (26%) had disease progression. The median PFS was 3.7 months (95% CI, 3.2-4.7 months, Figure 1). The 6-month and 1-year PFS rates were 35% and 21%, respectively. Twenty-one of 70 patients (30%) remain alive. The median OS was 6.3 months (95% CI, 4.2-7.9 months; Figure 2). Overall survival rates at 6 months and 1 year were 50% and 24%, respectively. Among patients with a PS of 3 (n = 12), there was 1 PR (8%) and 7 patients who had SD (58%), resulting in a disease control rate of 67%. Data on second-line therapy were limited to 17 patients (24% of total enrolled) and therefore are not available for analysis.

Treatment-Related Toxicity

Sixty-six patients were assessable for toxicity. Toxicities attributed to gefitinib included fatigue/weakness, nausea/vomiting, dyspnea, diarrhea, rash, myalgias, anorexia, and anemia (Tables 5 and 6). Grades 2 and 3 fatigue/weakness occurred in 27 patients (41%) and 19 patients (29%), respectively. Grades 2 and 3 nausea/vomiting occurred in 4 patients (6%) and 3 patients (5%), respectively. Grades 2 and 3 dyspnea occurred in 9 patients (14%) and 5 patients (8%), respectively. Grade 2/3 anorexia was seen in 21% and 5% of patients, respectively. All remaining grade 3/4 toxicities, including rash and diarrhea, were seen in ≤ 3% of patients. Few grade 4 nonhematologic toxicities were observed (infection, dyspnea, and hypertension in 1 patient each; and deep vein thrombosis or pulmonary embolus in 2 patients). No grade 3/4 hematologic toxicities were seen; however, 13 patients (20%) had grade 2 anemia.

Quality of Life and Symptom Response Analysis

The FACT-L (QOL) and LCS (SR) questionnaires were completed by 70% and 67% of enrolled patients, respectively, at baseline; and by 39% and 53% of patients included in the response analysis, respectively (with sufficient entries to permit best overall response scoring, as outlined in Table 2). A small number of patients completed QOL or SR surveys beyond 2 cycles: 11 patients after 4 cycles; 6 patients after 6 cycles; and 3 patients after 8 cycles. On average, 82% of evaluable patients reported improvements or no change in QOL from baseline. Eighty-six percent, 82%, 87%, and 73% of patients reported improvements or no change in physical, social/family, emotional, and functional well-being, respectively (Table 7). Symptom response improvement, control, and worsened rates were 32%, 48%, and 47%, respectively; SR improvement and worsened rates were similar among patients with SD. Male patients accounted for 89% of patients with SD reporting worsening SR, whereas female patients represented 67% of patients with SD reporting SR improvement. There were too few responses to correlate with QOL or SR rates. Also, the limited number of patients completing surveys prevents the finding of any consistent correlation between the FACT-L and SR rates, or between these rates and survival. Finally, too few patients reported histories of nonsmoking (n = 2) for correlative studies in terms of QOL and SR. Reasons for noncompliance included patient preference, illness/death, or coming off study.

Table 5 Treatment-Related Nonhematologic Toxicity (n = 66)

Toxicity	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Fatigue	20 (30.3)	11 (16.7)	0
Weakness	7 (10.6)	8 (12)	0
Infection (including pneumonia, cellulites, and sinus infection)	4 (6.1)	1 (1.5)	1 (1.5)
Nausea	4 (6.1)	1 (1.5)	0
Vomiting	0	2 (3)	0
Diarrhea	10 (15.2)	2 (3)	0
Dyspnea/SOB	9 (13.6)	5 (7.6)	1 (1.5)
Arthralgia	1 (1.5)	0	0
Myalgia	3 (4.5)	1 (1.5)	0
Rash	8 (12)	2 (3)	0
Anorexia	14 (21.2)	3 (4.5)	0
Constipation	4 (6.1)	0	0
Mucositis	3 (4.5)	0	0
Cough	2 (3)	0	0
Hypotension	0	2 (3)	0
Hypertension	0	0	1 (1.5)
Dizziness	0	1 (1.5)	0
Dry Mouth	1 (1.5)	0	0
Eye Irritation	0	1 (1.5)	0
Headache	1 (1.5)	1 (1.5)	0
Taste Change	1 (1.5)	0	0
DVT/PE	0	1 (1.5)	2 (3)

Abbreviations: DVT = deep vein thrombosis; PE = pulmonary embolus; SOB = shortness of breath

Discussion

In this multicenter phase II trial, we evaluated the efficacy of the EGFR TKI gefitinib in the first-line treatment of advanced

Table 6 Grade 2 Treatment-Related Hematologic Toxicity (n = 66)*

Toxicity	Number of Patients (%)
Anemia	13 (19.7)
Leukopenia	0
Thrombocytopenia	0
Neutropenic Fever	0
Platelet Transfusion	0
RBC Transfusion	3 (4.5)
Epoetin Alfa or Exemestane	9 (13.6)

*There were no grade 3/4 toxicities.
Abbreviation: RBC = red blood cell

Table 7 Quality of Life Improvement, Control, and Worsened Rates

FACT-L (Well-Being)	Improvement Rate (%)	Control Rate (%)	Worsened Rate (%)
Physical	12	86	8
Social/Family	3	82	7
Emotional	5	87	14
Functional	14	73	9

NSCLC in patients with poor PS (ECOG PS 2/3). The overall response rate was 4%, and 46% of patients had SD, resulting in an overall disease control rate of 50% (the proportion of patients with objective tumor responses combined with the proportion with stable disease). The median PFS and OS rates were 3.7 months and 6.3 months, respectively.

Our trial represents the largest prospective study of first-line single-agent treatment with an oral EGFR TKI in advanced NSCLC. The purpose of this trial was to evaluate a novel, relatively well-tolerated oral therapy in patients with poor PS (≥ 2), a group often underrepresented in NSCLC clinical trials. Patients with poor PS have largely been excluded from clinical trials because of the substantial risks and limited expected benefit of chemotherapy treatment.[8-11] American Society of Clinical Oncology guidelines for the treatment of advanced NSCLC underscore the importance of patient selection and consideration of a good PS in treating patients with chemotherapy, cautioning selection of patients with a PS of 2.[1]

In a large randomized trial comparing 4 chemotherapy regimens in the first-line treatment of advanced NSCLC, a subset of patients with a PS of 2 experienced significant treatment-related toxicity and limited 1-year survival (19%).[12,13] This trial's enrollment of patients with a PS of 2 was later amended to exclude these patients. In another recent large prospective study comparing paclitaxel versus carboplatin/paclitaxel in the first-line setting, randomization was stratified by stage (IIIB vs. IV), age (≥ 70 vs. < 70 years), and PS (0/1 vs. 2).[14] Eighteen percent of patients had a PS of 2. Overall, fewer patients with a PS of 2 were alive at 1 year compared with patients with PS 0/1 (14% vs. 38%). These differences were seen in combination and single-agent treatment arms. Similarly, in a subset analysis (n = 130, 19%) of the Multicenter Italian Lung Cancer in the Elderly Study, which compared the combination of gemcitabine/vinorelbine versus either agent alone in elderly patients, patients with a PS of 2 had worse outcomes (response rate, time to progression, and survival) compared with patients with a PS of 0/1.[15,16] Combination therapy offered no advantage over single-agent treatment for this subset of patients.

Consequently, few prospective studies in advanced NSCLC have focused enrollment on patients with poor PS. More often, studies of patients not considered candidates for standard platinum agent–based doublet regimens have defined enrollment by age rather than PS. In these trials, patients with a PS of 2 account for a minority of patients, and patients with a PS of 3 are often excluded altogether. Currently, there is no standard chemotherapy regimen for patients with a poor PS. A European Experts Panel recently concluded that several single-agent and combination regimens may be appropriate in patients with a PS of 2.[17] Available evidence for patients with a of PS 2 suggests chemotherapy results in a median survival of 3-5 months and a 1-year survival rate of 18%-20%.[14,15,18,19] Our study demonstrated similar efficacy with single-agent gefitinib as first-line therapy.

Our study also demonstrated that gefitinib can be administered safely to patients who have a poor PS with advanced NSCLC. Grade 3/4 toxicity was primarily limited to fatigue and weakness, which more likely reflect patient PS. Consistent with the majority of gefitinib trials to date, rash and diarrhea were seen, but grade 3/4 toxicity was minimal. Importantly, gefitinib was associated with improvements or no change in disease-related symptoms and QOL as reported by 48% and 82% of patients, respectively.

These results are consistent with those from other phase II trials in NSCLC with gefitinib.[5,6] In 2 large monotherapy trials, gefitinib was given to patients with advanced NSCLC who had received ≥ 1 previous platinum agent–based regimen. The disease control rates for each trial were 54% and 42%, respectively, with toxicities limited to grade 1/2 rash and diarrhea. Symptom improvement in these trials correlated with disease control, and median survival ranged from 7 to 8 months. The median ages of patients enrolled in these 2 trials were 61 and 62 years, respectively; and the percentages of patients with a PS of 0/1 were 87% and 80%, respectively.

Two first-line monotherapy NSCLC studies with gefitinib have been reported. Twenty-five patients with advanced NSCLC received first-line gefitinb in an expanded access program.[20] Patients were eligible if they had a poor PS or refused chemotherapy. Eighty-one percent of patients had a PS of 2 and the median age was 73 years old. The disease control rate was 36% and toxicity was limited to diarrhea and rash. The median PFS and OS were 2.9 months and 14.1 months, respectively. Similarly, 22 patients deemed unfit (56%; PS > 2) or who refused chemotherapy received gefitinib as a part of a compassionate use program.[21] The disease control rate in this small phase II study was 41%, and median PFS and OS were 2.2 months and 12.6 months, respectively. Recently, preliminary results were reported from a phase II trial looking at the role of

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