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ORIGINAL ARTICLE

Body mass index and exon 19 mutation as factors predicting the therapeutic efficacy of gefitinib in patients with epidermal growth factor receptor mutation-positive non-small cell lung cancer

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Keywords
Body mass index (BMI); CART; EGFR active mutation; gefitinib; non-small-cell lung cancer.

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Abstract

Background: Many randomized clinical trials have demonstrated that epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are advantageous over standard chemotherapy, either as front-line treatment or as further management of patients with EGFR mutation-positive non-small-cell lung cancer (NSCLC). However, which subgroup of these patients could benefit more from EGFR-TKIs needs to be further explored. In the present study, we explored the predictive factors in such cohorts of patients who received gefitinib.

Methods: The study included 95 patients with EGFR mutation-positive advanced NSCLC who received gefitinib treatment. Multivariate analysis of progression-free survival (PFS) was performed using classification and regression tree (CART) analysis to assess the effect of specific variables on PFS in subgroups of patients with similar clinical features.

Results: The median PFS in patients with EGFR mutation-positive advanced NSCLC who received gefitinib treatment was 13.3 months (95% confidence interval 9.4–17.2). CART analysis showed an initial split on body mass index (BMI); subsequently, three terminal subgroups were formed. The median PFS in the three subsets ranged from 8.2 to 15.2 months, in which the subgroup with a BMI less than or equal to 20.8 kg/m^2 had the longest PFS (15.2 months). In addition, PFS in the EGFR exon 19 mutation group was better than in the other mutation site group (10.3 vs. 8.2 months).

Conclusions: BMI and exon 19 mutation may be predictors of PFS in patients with EGFR mutation-positive advanced NSCLC who receive gefitinib treatment. Both active EGFR mutation and patient-specific factors may be used to predict the therapeutic efficacy of EGFR-TKIs.

Introduction

The epidermal growth factor receptor (EGFR), as part of the signaling pathway that regulates tumor cell proliferation, invasion, angiogenesis, metastasis, and apoptosis, is frequently overexpressed in non-small cell lung cancer (NSCLC).[1,2] Lynch *et al*. reported that there was a close correlation between specific EGFR mutation and the benefit of gefitinib in advanced NSCLC patients.[3] The IPASS study reported that certain subgroups of patients (Asian, with adenocarcinoma histology, female, and never-smoking status) benefited more from gefitinib treatment.[4] The latest IPASS data has proven that EGFR mutation is the strongest predictive biomarker for progression-free survival (PFS) and tumor response.

Based on these findings, at least eight clinical trials enrolled NSCLC patients with active EGFR mutations. The OPTIMAL study conducted by Zhou *et al*. reported that the median PFS was significantly longer in erlotinib-treated patients than in chemotherapy group patients (13.1 vs. 4.6 months; hazard ratio [HR] 0.16).[5] Mitsudomi *et al*. reported that the median PFS in their gefitinib group was significantly longer than in their cisplatin plus docetaxel group (9.2 vs. 6.3 months, $P < 0.0001$).[6] NEJ002 reported similar results.[7]

The IDEAL1 study reported that the objective response rate of 250 mg/day of gefitinib was 18.4% and a higher dose (500 mg/day) did not seem to improve the response; the recommended dosage of 250 mg of gefitinib per day did not take physical size, such as body mass index (BMI) and body surface area (BSA), into account.[8]

Many randomized controlled trials have shown that epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) could provide significant benefits in patients with EGFR mutation-positive advanced NSCLC, but it is unclear which subgroup of patients with EGFR mutation could benefit more from gefitinib treatment. In this retrospective study, we analyzed the clinical data of 95 patients with EGFR mutation-positive advanced NSCLC in an attempt to identify the subgroup that can benefit more from EGFR-TKIs.

Patients and methods

Patients who had been histologically or cytologically confirmed as having stage IV NSCLC with active EGFR mutation and treated with gefitinib at the Cancer Institute (Hospital) of the Chinese Academy of Medical Sciences (Beijing, China) between February 2010 and October 2013 were eligible for enrollment into this study. All active EGFR mutations were assessed by direct sequencing. The enrolled patients had measurable or evaluable indicator lesions. Patients were excluded if they had previously been treated with monoclonal antibodies or small molecule inhibitors of EGFR, such as C225 and erlotinib. In addition, patients with radiologically and clinically confirmed interstitial pneumonitis or pulmonary fibrosis were not eligible.

Responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).[9]

The primary end point was median PFS, which was defined as the interval from the initial gefitinib administration to objective disease progression (as per RECIST) or the date of any cause of death. Patients not experiencing an event were censored at the last date of follow-up for PFS.

Statistical considerations

Progression-free survival was estimated using Kaplan–Meier analysis. Median PFS was computed as the time when the Kaplan–Meier estimate crossed 50%. Multivariate analysis of PFS was performed using recursive partitioning, referred to as classification and regression tree (CART) analysis. CART analysis was also used to identify optimal cut-off points in the data. Clinical variables were analyzed within the following general categories: mutation site, smoking history, BMI, BSA, sample location, timing of treatment, and involvement of specific metastatic sites.

Results

Patient characteristics

In this retrospective study, 95 patients treated with gefitinib satisfied our inclusion criteria. Additional details are summarized in Table 1. At the cut-off date (1 January 2014), the median follow-up duration was 15.8 (2.8–47) months. Of the 95 patients included, 38 patients were still in clinical benefit status. The median age of the 95 patients was 57 (30–77) years and most of the patients ($n = 64$) were women. All 95 patients were histologically confirmed as having adenocarcinoma

Table 1 Demographic and tumor-related characteristics of 95 patients

Parameter	No. of patients	%
Age (median, year)	57	30–77
BMI (kg/m^2)	24.05	15.81–34.48
Gender		
Female	64	67.4
Male	31	32.6
Pathologic variables		
Adenocarcinoma	95	100
Non-adenocarcinoma	0	0
Location of sample		
Primary lesion	77	81.1
Metastatic lesion	18	18.9
Smoking history		
Never smoked	71	74.7
Ex-smoker or current smoker	24	25.3
Timing of treatment		
First-line	47	49.4
Subsequent	48	50.5
Involvement of metastases sites		
Brain	13	13.7
Liver	8	8.4
Bone	38	40
Adrenal	4	4.2
Pulmonary	41	43.2
Other sites	41	43.2
EGFR mutation status		
18	2	2.1
19	49	51.6
20	13	13.7
21	44	46.3

BMI, body mass index; EGFR, epidermal growth factor receptor.

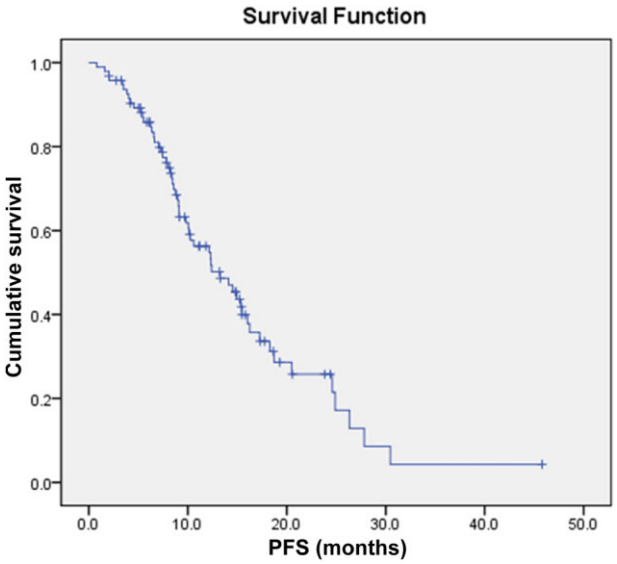

Figure 1 Kaplan–Meier curves for progression-free survival (PFS) in 95 patients. (⌐¬) Survival function, (+) Censored.

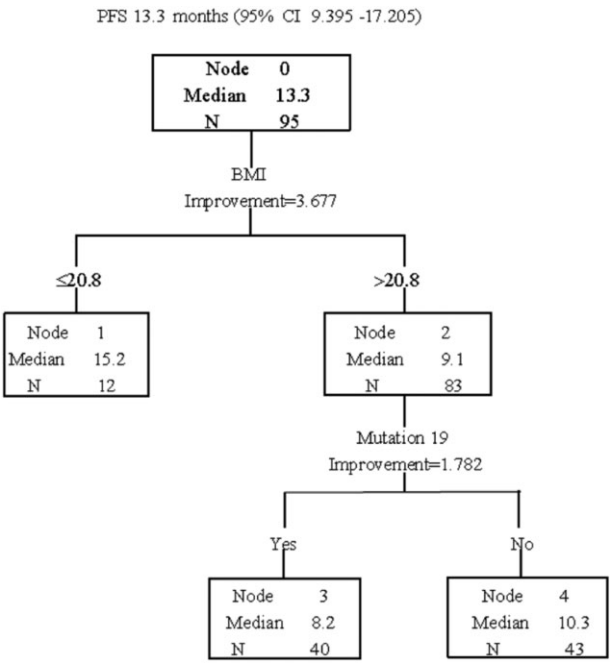

Figure 2 Classification and regression tree generated with the initial split on body mass index (BMI). CI, confidence interval.

with EGFR mutation, including multisite mutation in 12 patients.

Survival

The median PFS was 13.3 months (95% confidence interval 9.4–17.2) (Fig 1).

Classification and regression tree analysis

CART analysis was performed using clinical variables. A default tree was generated using the CART program to determine the variable with the optimal first split. The initial split was BMI, followed by EGFR exon 19 mutation. These variables generated the CART structure, whereby three terminal subgroups were produced (Fig 2). The median PFS was significantly different between the three subgroups. PFS curves are shown in Figure 3. The overall comparisons showed $P = 0.014$ (Fig 3). The subgroup with BMI less than or equal to 20.8 kg/m^2 had the longest PFS (15.2 months). The PFS in the EGFR exon 19 mutation group was better than in the other site mutation group (10.3 vs. 8.2 months).

Discussion

Some clinical trials have demonstrated that patients with EGFR mutation-positive tumors had better outcomes in terms of PFS and overall response rate with gefitinib.[3,5,7,10–12] In NEJ002, the median PFS of gefitinib was 10.8 versus 5.4 months in the chemotherapy group.[7] In the OPTIMAL study, the median PFS in the erlotinib group was significantly longer than in chemotherapy group, with PFS rates of 13.1 versus 4.6 months.[5]

To determine whether active EGFR mutation was strongly correlated with responsiveness to EGFR-TKIs and which subgroup could benefit more from EGFR-TKIs, all NSCLC patients with EGFR mutation were administered EGFR-TKIs as front-line treatment; although not all NSCLC patients with EGFR mutation could benefit equally from gefitinib treatment. Our CART analysis showed that the initial split was BMI. It is common knowledge that BMI is defined as weight in kilograms divided by the square of the height in meters, and BMI groups are defined by the World Health Organization as underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5 to < 25 kg/m^2), overweight (BMI 25 to < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2).[13]

Clinical dosing of a cytotoxic drug depends on the therapeutic window because the toxic effect and anti-tumor activity often fall within the same dose range.[14] However, EGFR-TKIs are cytostatic, and the optimum biological dose (OBD) is much lower than the maximum tolerated dose (MTD). Although the objective tumor response could be observed at a dose of 150 mg/day, the IDEAL1 trial chose 250 mg/day and 500 mg/day to avoid inter-patient variability in pharmacokinetics. The disease control rate was 54.4% and 51.4%, respectively. The PFS was 2.7 months in the 250 mg/day group and 2.8 months in the 500 mg/day group. As the higher dose did not provide a better response and the terminal half-life was approximately 48 hours in patients with NSCLC, 250 mg of

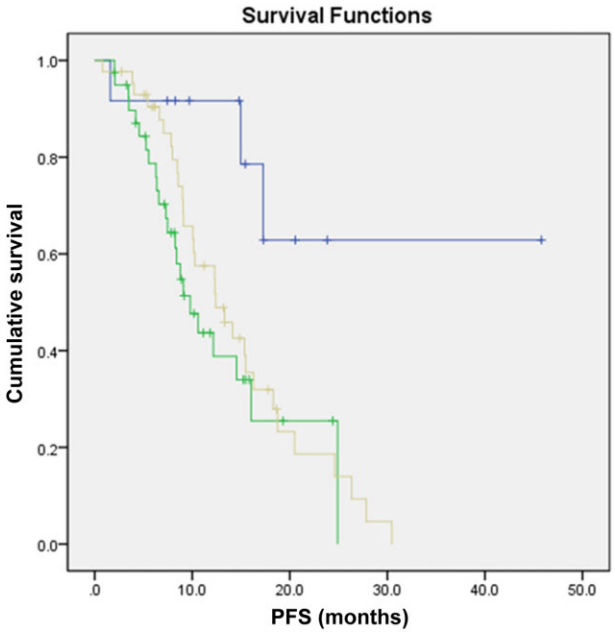

Figure 3 Kaplan–Meier survival curves of the three terminal subgroups generated from classification and regression tree analysis. Group: (—) 1.00, (—) 3.00, (—) 4.00, (—) 1.00-censored, (—) 3.00-cnesored, (—) 4.00-censored. Node 1: body mass index (BMI) less than or equal to 20.768 kg/m^2. Node 3: BMI greater than 20.768 kg/m^2 and without exon 19 mutation. Node 4: BMI greater than 20.768 kg/m^2 and with exon 19 mutation.

gefitinib is suitable for once daily dosing, and steady-state exposure is achieved after 10 days.[15,16]

The CART tree showed that patients with a BMI of less than or equal to 20.8 kg/m^2 had the longest PFS compared to those with a BMI greater than 20.8 kg/m^2 (15.2 vs. 9.1 months). A previous study reported that physical size may also affect pharmacokinetics.[17] In Ichihara *et al*.'s study, the median PFS of the patients with a higher BSA (≥ 1.5 m^2) was significantly worse than those with a lower BSA (< 1.5 m^2) (10.4 vs. 18.0 months, $P = 0.019$).[18] A study on imatinib and BSA showed that reducing the dose of imatinib could maintain an effective blood concentration in a lower BSA group.[19]

In a trial measuring the plasma trough levels of gefitinib on days three (D3) and eight (D8) by high-performance liquid chromatography in 23 EGFR mutation advanced NSCLC patients treated with 250 mg gefitinib daily, the D8/D3 ratio was considered to be the slope of the graph of the plasma concentration of gefitinib until a steady state was reached.[20] The median PFS in the high D8/D3 ratio group ($n = 13$) was 336 vs. 38 days in the low D8/D3 rate group ($n = 10$). It remains unclear whether or not increasing the dose of gefitinib could improve the efficacy in patients with EGFR mutation who have high metabolism with gefitinib.

A previous trial observed that inter-patient variability could affect the plasma concentration of gefitinib and its anti-tumor activities.[15] Although 250 mg of gefitinib is suitable for once daily dosing, some factors could affect the metabolism of gefitinib, such as the pH of gastric juice and increased enzymatic expression.

The initial split urged us to consider the importance of dose adjustment by BMI, with the knowledge that there is a correlation between BMI and pharmacokinetics.

Epidermal growth factor receptor mutation status is the most important determinant of response to TKI.[4,21] EGFR mutation includes exons 18, 19, 20 and 21. Deletion of exon 19 and L858R mutation in exon 21 are the most common mutations.[21] Exon 18 and 20 are rarely mutated.

Our last split was the exon 19 mutation. PFS was better in patients with exon 19 mutation than in patients with mutations in other sites (10.3 vs. 8.2 months). Analysis of LUX-Lung 3 and LUX-Lung 6 in two randomized trials showed that first-line afatinib significantly improved overall survival (OS) in patients with EGFR exon 19 deletion, but not in patients with L858R mutation.[22] Combined analysis showed that OS in the exon 19 deletion and chemotherapy groups was 31.1 and 20.7 months (P=0.0001), respectively, versus 22.1 and 26.9 months in the L858R mutation and chemotherapy groups ($P = 0.16$), respectively. OS in the exon 19 deletion group was better than in the exon 21 mutation group of patients who were administered gefitinib. Jackman *et al*. reported that patients with an exon 19 deletion had a longer median time to progression and OS compared with patients harboring an L858R mutation (14.6 vs. 9.7 months, and 30.8 vs. 14.8 months; $P < 0.001$).[23] A retrospective study reported that patients with an exon 20 mutation had the shortest median PFS (2.1 months), followed by those with double mutations (4.2 months), exon 21 mutations (10.6 months), and exon 19 deletions (12.8 months), although they found that not all exon 19 mutation subtypes had an equally favorable response to EGFR-TKIs.[24] Therefore, exon 19 mutation as the split is convincing.

One of the limitations of our study is that BMI data were not updated because the patients received gefitinib on an outpatient basis; therefore, we obtained patient height and weight data from hospital records, which may, in turn, bias the results.

Conclusion

Classification and regression tree programs effectively segregate patients into different groups with similar clinical features in terms of survival. Patients with a lower BMI and exon 19 mutation seem to benefit more from treatment with gefitinib.

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Disclosure

No authors report any conflict of interest.

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