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ORIGINAL ARTICLE

Classification and regression tree analysis of patients with non-small-cell lung cancer treated with gefitinib after chemotherapy

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Abstract

Background: Many randomized studies have shown that epidermal growth factor receptor (EGFR-) tyrosine kinase inhibitors (TKIs) are apparently advantageous over standard chemotherapy in non-small-cell lung cancer (NSCLC) patients with EGFR active mutation in front-line treatment. But which subgroup of advanced NSCLC could benefit from EGFR-TKIs in the second-or third-line setting remains elusive. To explore predictive factors of advanced NSCLC patients with the unknown status of EGFR mutation treated by gefitinib in the second-or third-line setting, we used classification and regression tree (CART) analysis to screen which patients would benefit more.

Methods: One hundred and fifty-five patients with advanced NSCLC previously unsuccessfully treated with platinum-based chemotherapy were included in this study. Patients received gefitinib as part of the Expanded Access Program of the China Charity Federation between 2 March 2005 and 11 May 2011. Multivariate analysis of progression-free survival (PFS) was performed using CART analysis. This method uses recursive partitioning to assess the effect of specific variables on PFS, thereby ultimately generating groups of patients with similar clinical features on PFS.

Results: The median PFS in patients with NSCLC who were treated with gefitinib after prior chemotherapy was 16 months (95% confidence interval [CI] 13.44–18.56). CART was performed with an initial split on adenocarcinoma differentiation, and four terminal subgroups were formed. The median PFS of the four subsets ranged from 12 to 42 months.

Conclusions: Adenocarcinoma differentiation, brain metastasis and prior thoracic radiotherapy are predictors of PFS in previously treated NSCLC patients. CART can be used to identify homogeneous patient populations in clinical practice and future clinical trials.

Introduction

Chemotherapy is one of the mainstays of treatment for local advanced or metastatic non-small cell lung cancer (NSCLC). The median overall survival of the current generation of platinum-based first-line chemotherapy for NSCLC is seven to 10 months.[1–3] In a prospective randomized trial,[4] the median overall survival was 7.5 months versus 4.6 months using single-agent docetaxel in second-line treatment, compared with best supportive care. Hanna *et al*[5] reported that the median progression-free survival (PFS) was 2.9 months in patients with advanced NSCLC using pemetrexed as second-line therapy, which is identical to that of the control (single-agent docetaxel). The median survival was not significantly different between the two groups (8.3 vs. 7.9 months) ($P = 0.05$). Generally speaking, second-line chemotherapy can improve one-year survival by 10%. But, unfortunately, Gaafar *et al*. reported that some NSCLC patients lost the opportunity to receive salvage therapy as a result of poor performance status (PS) and comorbidities.[6] A retrospective

analysis by Massarelli *et al.*[7] showed that third-line chemotherapy provided little benefit, as they reported that the median survival from the commencement of the last treatment was only four months.

The epidermal growth factor receptor (EGFR) forms part of the signaling pathway that regulates tumor-cell proliferation, invasion, angiogenesis, metastasis, and apoptosis. It is frequently overexpressed in NSCLC.[8,9] Lynch *et al*[10] found that there is a close relationship between specific EGFR mutation and the benefit of gefitinib in advanced NSCLC. Gefitinib is an orally available reversible inhibitor of the tyrosine kinase domain of the EGFR, with tolerable adverse events. Certain subgroups of patients (oriental, female, never-smokers or with adenocarcinoma histology) showed better clinical benefits.[11–14]

Many randomized studies have shown that EGFR tyrosine kinase inhibitors (TKIs) could offer significant benefits in advanced NSCLC patients with an EGFR mutation-positive status, not only in first-line treatment, but also in the maintenance setting. In an INTEREST study,[15] there was no significant difference between gefitinib and docetaxel groups in the second-line setting nor was there conclusive data to support the difference between the two arms, in terms of the EGFR mutation status. In fact, the EGFR mutation status is not a compulsory guideline for second- or third-line treatment in clinical practice. In the present study, we analyzed the clinical data of 155 patients with advanced NSCLC whose previous platinum-based chemotherapy had failed, to predict which patient group with an unknown EGFR mutation status could benefit more from EGFR-TKIs.

Patients and methods

Patients who had been histologically or cytologically confirmed as having stage IIIB/IV NSCLC and had undergone at least one platinum-based chemotherapy, were eligible for enrolment into this study. All of the enrolled patients had measurable or evaluable indicator lesions and had achieved clinical benefits after receiving gefitinib for at least six months. Patients with brain metastasis were still considered eligible if they had received brain radiation therapy and had stable disease. 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 apparent interstitial pneumonitis or pulmonary fibrosis were not eligible.

Responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).[16]

The primary end point was median PFS, which was defined as the interval from the time of taking gefitinib to objective disease progression (as per RECIST[16]) or the date of any cause of death.

Statistical considerations

The PFS was estimated using a 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 points in the data. Fifteen clinical variables were analyzed within the following general categories: demographic variables, smoking history, pathological and differentiation variables, involvement of specific metastasis sites, the number of comorbidities, and prior thoracic radiotherapy.

Results

Patient characteristics

In this retrospective study, 155 patients whose previous platinum-based chemotherapy had been unsuccessful satisfied our inclusion criteria. The baseline patient demographics are listed in Table 1. The time point of their last follow-up was treated as the time of events (disease progression) if patients were lost to their follow-ups. At data cut-off (1 February 2012), the median follow-up duration was 21.6 (9–79.3) months. Thirty-two patients were still in the clinical benefit status. The median age was 55 (22–79) years. Most of the patients were female (114, 73.5%) and never-smokers (117, 75.5%); 151 (97.4%) were histologically confirmed as having adenocarcinoma; and 114 (73.5%) had previously received taxane-based chemotherapy.

Survival

The median PFS was 16 months (95% confidence interval [CI] 13.44–18.56) (Fig. 1).

CART analysis

CART was performed using 15 clinical variables. The structure of each tree depended on the initial split of the patients. A default tree was generated by allowing the CART program to determine the variable with the optimal first split. CART was performed with an initial split on adenocarcinoma differentiation, followed by brain metastasis and prior thoracic radiotherapy. These variables generated the CART structure. According to the analysis, four terminal subgroups were produced (Fig. 2). There were statistically significant differences among the four subgroups. The median PFS was significantly different between the four terminal subgroups. The overall comparisons showed $P = 0.011$. PFS curves are shown in Figure 3. The longest PFS subgroup was found in patients with well-differentiated adenocarcinoma without brain

Table 1 Demographic characteristics and tumor-related characteristics of 155 consecutive patients

Parameter	No. of patients	%
Age (median, year)	55	22 to 79
Gender		
Female	114	73.5
Male	41	26.5
Pathologic variables		
Adenocarcinoma	151	97.4
Adenocarcinoma	85	54.9
Well- differentiated adenocarcinoma	32	20.6
Moderately- poor-differentiated adenocarcinoma	34	21.9
Non- Adenocarcinoma	0	0
Not otherwise specified (NOS)	4	2.6
Smoking history		
Never smoked	117	75.5
Ex-smoker or Current smoker	26	16.8
No exact detail	12	7.7
Lymph node		
N0	53	34.2
N1	3	1.9
N2	58	37.4
N3	41	26.5
Involvement of metastases sites		
Lung	68	43.9
Pleural	58	37.4
Brain	37	23.9
Liver	9	5.8
Other sites	5	3.2
No. of comorbidities		
0	100	64.5
1	31	20.1
2	21	13.5
3 or more	3	1.9
Thoracic radiotherapy history		
Yes	46	29.7
No	109	70.3

metastasis, and who had received prior thoracic radiotherapy; their median PFS was 42 months. The PFS of the subgroup of patients with moderately and poorly differentiated adenocarcinoma was very poor (12 months). The adenocarcinoma differentiation, brain metastasis, and prior thoracic radiotherapy had a great impact on survival. The PFS of the well-differentiated adenocarcinoma subgroup was better than that of the moderately-poorly differentiated adenocarcinoma (18 months vs.12 months). Patients without brain metastasis had a better survival rate than those with brain metastasis (19 months vs.13 months). Prior thoracic radiotherapy was a good predictor for EGFR-TKIs.

Discussion

Chemotherapy remains the mainstay of treatment for advanced NSCLC. Platinum-based doublets are recommended for fit patients, and single agents can be offered in elderly patients or poor performance subsets[17] in the first-line setting; the median survival rate for these groups is approximately 7–10 months.[1–3] Using docetaxel as the standard second-line treatment option available, the median survival is 7.5 months versus 4.6 months for best supportive care alone.[4] Patients with advanced NSCLC are often symptomatic, with specific pulmonary and general symptoms including cough, breathlessness, fatigue, and weight loss, which can cause extreme distress. Therefore, improvements in disease-related symptoms and quality of life are the key desired outcomes of medical management.[18] Effective, palliative, low-toxicity treatments for patients with advanced NSCLC are required.

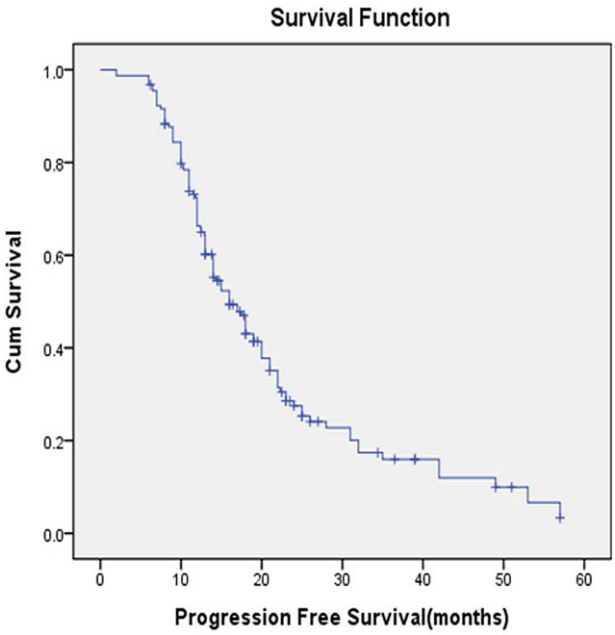

Figure 1 Kaplan-Meier curves for progression-free survival (PFS) in 155 patients. The median PFS was 16 months; 95% confidence interval (CI), 13.44–18.56 months. —⌐, Survival Function; —|—, Censored.

In randomized phase 2 trails (IDEAL 1), the response rate (RR) in patients treated with gefitinib at 250 mg/d was 18.4%, the median PFS was 2.7 months, and the median overall survival (OS) was 7.6 months, suggesting that gefitinib is an effective treatment for previously treated patients with advanced NSCLC.[13] A trial[12] comparing gefitinib with the placebo in the second- and third-line setting did not show significantly increased survival in the overall population. However, significant benefits were seen in lifetime non-smokers and patients of Asian origin. In BR21, erlotinib was compared with the placebo in the second- and third-line setting for advanced NSCLC. Treatment with erlotinib was associated with a significant extension of survival and a delay in the time to deterioration of symptoms.[19] Our results showed significant prolongation of PFS (median PFS 16

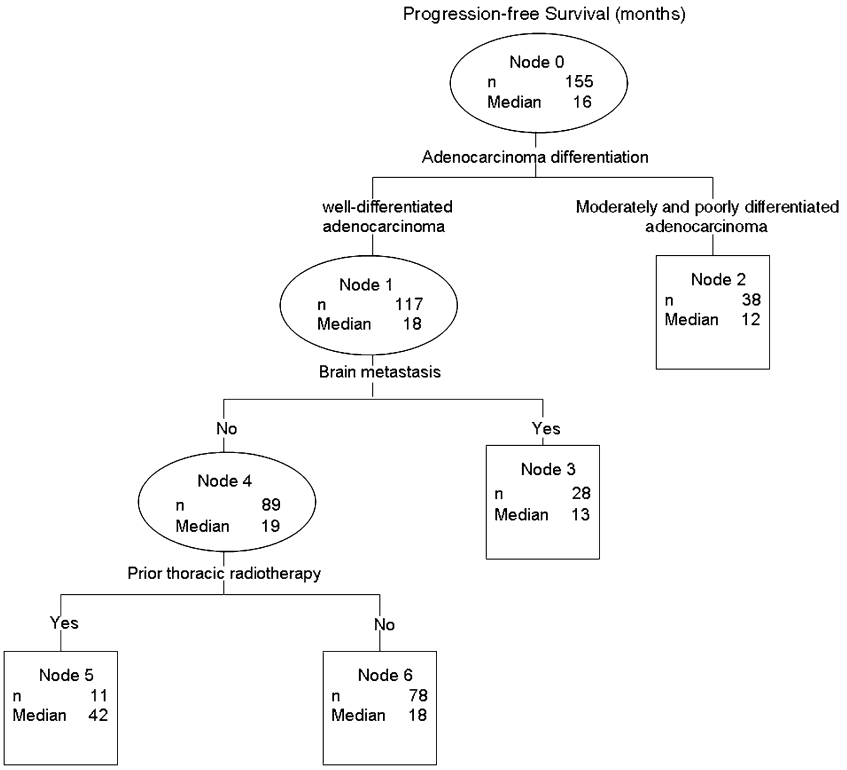

Figure 2 Classification and regression tree (CART) generated with the initial split on adenocarcinoma differentiation.

months,) as compared with the historic data of best supportive care. Although the EGFR mutation status was unknown, numerous trials[6,12,15,20–23] have proved that patients with EGFR mutation-positive tumors have a better outcome with gefitinib, in terms of PFS and overall response rate (ORR). Some investigators have reported that responsiveness to EGFR inhibitors correlates with sex, histological type, ethnic origin, and smoking status. It is very difficult to screen patients who satisfy all of these clinical variables. In INTEREST study, there is no significant difference between gefitinib and docetaxel groups in the second-line setting nor is there conclusive data to support the difference between the two arms, in terms of the EGFR mutation status. So far, the EGFR mutation status could not guide clinical practice in the second- or third-line setting.

Our CART analysis showed that the initial split is adenocarcinoma differentiation. The PFS was 18 months and 12 months in patients with well-differentiated tumors and those with moderately-poorly differentiated tumors, respectively. Barletta *et al.*[24] found that the main difference in overall survival was between patients with poorly differentiated tumors and those with well or moderately differentiated tumors. The results of their study are consistent with the findings reported in previous studies.[25,26] In fact, this phenomenon implies that mutations are more prevalent in well-differentiated adenocarcinomas than those in moderate-poor differentiated adenocarcinomas.[27] Adenocarcinoma differentiation as the initial split of the CART tree is convincing.

Some studies[28,29] have shown that brain metastasis is a poor variable – 30–50% NSCLC patients with brain metastases had a worse prognosis and quality of life. The median survival of patients who received best supportive care and corticosteroids alone is approximately one to two months.[30] Primary approaches to the treatment of brain metastases include whole-brain radiation therapy (WBRT), stereotactic radiosurgery, surgery or a combination, which have achieved a median survival ranging from 6.5 months to 10 months.[31,32] Fortunately, Eichler *et al.*[33] reported that patients with brain metastases from EGFR-mutant NSCLC had improved overall survival as compared with EGFR wild-type tumors when an EGFR inhibitor was received. In addition, Kim *et al.*[34] reported that a 70% central nervous system (CNS) response rate was observed in 23 Asian never smokers with brain metastases from NSCLC receiving first-line gefitinib or erlotinib. Patients with brain metastasis could also benefit from taking gefitinib if they are EGFR-mutation positive, though brain metastasis remains a negative factor.

The last split is thoracic radiotherapy. The NSCLC Collaborative Group meta-analysis[35] and the meta-analysis of platin-based concomitant chemotherapy in NSCLC[36] demonstrated that chemotherapy, in combination with radiotherapy, improved survival in locally advanced NSCLC.

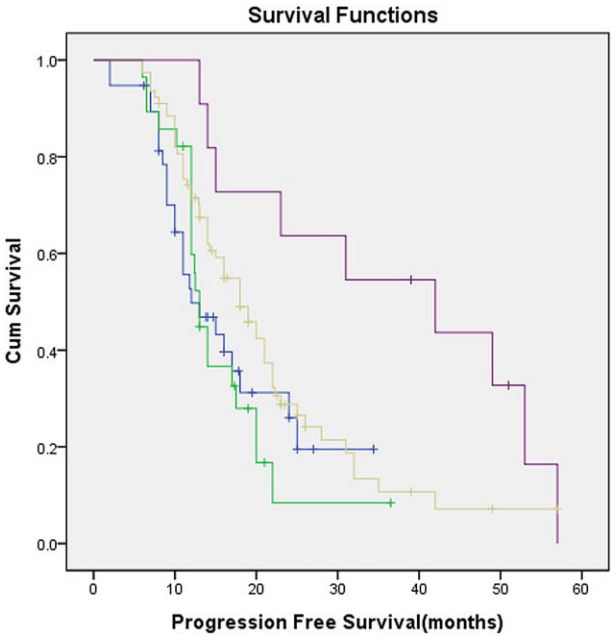

Figure 3 Kaplan-Meier survival curves of the four terminal subgroups generated from the default classification and regression tree (CART) analysis. Subgroup 1, patients with moderately-poorly differentiated adenocarcinoma. The median progression-free survival (PFS) was only 12 months. Subgroup 2, patients with well-differentiated adenocarcinoma and brain metastasis. The median PFS was 13 months. Subgroup 3, patients with well-differentiated adenocarcinoma without brain metastasis, did not receive prior thoracic radiotherapy. The median PFS was 18 months. Subgroup 4, patients with well-differentiated adenocarcinoma without brain metastasis, who had received prior thoracic radiotherapy. The median PFS was 42 months. The overall comparisons shows $P = 0.011$. , 1; , 2; , 3; , 4; , 1-censored; , 2-censored; , 3-censored; , 4-censored.

Aupérin *et al.*[37] reported that concomitant radiochemotherapy was apparently beneficial to overall survival, with an absolute benefit of 5.7% (from 18.1% to 23.8%) at three years and 4.5% at five years. It is generally accepted that combinations would improve survival because of decreased distant metastasis and local control. Some patients in our study suffered from local advanced NSCLC. This partially explains why patients with prior radiochemotherapy benefited more from the treatment. We hypothesize that thoracic radiotherapy in NSCLC patient is a viable option.

Some investigators have reported that responsiveness to EGFR inhibitors correlates with female, adenocarcinoma, Asians, and smoking history factors.[11,13,19] Notably, our CART study did not treat these factors as splits. The reason why these factors did not emerge as key points is that most of the eligible patients who benefited from gefitinib for at least six months were female (114, 73.5%), adenocarcinoma patients (151, 97.4%), never smokers (117, 75.5%), and Asians (155, 100%). We could not find superior factors in patients with a dominant position.

CART programs effectively segregate patients into different groups with similar clinical features in terms of survival. CART is a useful method for dissecting complex clinical situations and identifying homogeneous patient populations.

Conclusion

In summary, the CART tree shows that patients with well-differentiated adenocarcinoma without brain metastasis who have received prior thoracic radiotherapy in combination with chemotherapy could benefit more from EGFR-TKIs in second- or third-line chemotherapy as per the Expanded Access Program (EAP).

Disclosure

No authors report any conflict of interest.

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