# Wood-Smoke Exposure as a Response and Survival Predictor in Erlotinib-treated Non-small Cell Lung Cancer Patients

# An Open Label Phase II Study

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**Introduction:** Erlotinib, a tyrosine kinase inhibitor, has improved survival and quality of life in patients with non-small cell lung cancer (NSCLC) after first- or second-line chemotherapy. Asian origin, adenocarcinoma histology, female gender, lack of tobacco use, and expression of epidermal growth factor receptor are significant independent predictors of response to Erlotinib. Although tobacco use is considered a major cause of NSCLC, other risk factors such as wood-smoke exposure (WSE) are associated. Almost 3 billion people worldwide rely on solid fuels as their primary source of domestic energy for cooking and heating.

**Methods:** In this study, 150 consecutive unselected patients with histologically proven NSCLC with progression after prior first- or second-line chemotherapy and/or poor performance status were treated with Erlotinib 150 mg/d. Clinical and pathologic characteristics were associated with response.

**Results:** Overall response to Erlotinib was observed in 51 patients [34%; 95% confidence interval  $\{95\% \text{ CI}\}$ , 29.9-37.6]. In multivariate analysis, clinical features associated with response to Erlotinib were adenocarcinoma (35 versus 20%; p=0.05) and WSE (83 versus 13%; p<0.001). Factors associated with longer progression-free survival in Cox analysis included adenocarcinoma (7.9 versus

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2.3 months; p = 0.009), female gender (8.4 versus 5.3 months; p = 0.04), and WSE (17.6 versus 5.3 months; p = 0.006).

**Conclusions:** WSE is associated with better response to Erlotinib and improved progression-free survival in patients with NSCLC. Additional studies in epidermal growth factor receptor signaling pathway in WSE-associated NSCLC are warranted.

**Key Words:** Erlotinib, Non-small cell lung cancer, Response predictor, Survival predictor, Wood-smoke exposure.

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ung cancer is the leading cause of cancer-related deaths worldwide. In 2007, the estimated incidence in the United States was 213,380 with 160,390 deaths. In 2002, 8044 new cases and 8255 deaths were reported in Mexico.<sup>2</sup> Although tobacco use is considered a major cause of non-small cell lung cancer (NSCLC), other etiologic factors have been proposed for its development, including radon exposure, cooking fumes, asbestos, heavy metals, human papillomavirus infection, and genetic susceptibility. Wood dust is designated as a human carcinogen and a risk factor for lung cancer.<sup>3</sup> Wood is burned for heating and cooking or just for pleasure in many homes worldwide. Almost 3 billion people rely on solid fuel (biomass and coal) as their primary source of domestic energy. Most of them live in developing countries but there are also many living in countries with a cold climate, such as those in Northern Europe.<sup>4</sup> In addition North Americans, particularly in Canada and the northwestern and northeastern sections of the United States, have increasingly turned to woodburning as an alternative method for domestic heating because of increasing energy costs.<sup>4,5</sup>

Wood-smoke exposure (WSE) for >50 years has been associated with increased risk of lung cancer as compared with pulmonary tuberculosis, interstitial lung disease, and miscellaneous pulmonary conditions [odds ratio, 1.9; 95% confidence interval {CI}, 1.1–3.5] after adjusting for age,

education, socioeconomic status, and tobacco smoke exposure.<sup>6</sup> Pathophysiologic mechanisms in the development of WSE-associated NSCLC remain unknown to date. Wood byproducts, such as benzene, 1,3-butadiene, formaldehyde and acetaldehyde are known carcinogens.<sup>4</sup> Macrophage dysfunction and increased activity of matrix metalloproteinases, specifically MMP-2 and -9 have been reported. Several studies have demonstrated that WSE could increase phospho-p53 protein. These changes could be similar to those caused by tobacco smoke.<sup>7</sup>

Chemotherapy, alone or in combination with radiation therapy, is the standard treatment for advanced NSCLC. With current first-line platinum-based chemotherapy schemes, median survival is 7 to 10 months.8-10 Docetaxel or Pemetrexedbased regimens are the current standard for second-line chemotherapy in NSCLC, exhibiting a 6 to 9% response rate (RR) and median survival time of 6 to 8 months. 11-13 However, improvements in chemotherapy for advanced NSCLC have reached a plateau. Advances in understanding the molecular basis of cancer biology have led to the discovery of several potential molecular targets, such as the epidermal growth factor receptor (EGFR), a tyrosine kinase (TK) receptor of the ErbB family that is usually altered in epithelial tumors.14 It mediates cell proliferation, differentiation, survival, angiogenesis, and migration, 15 and is overexpressed in 40 to 80% of NSCLC tumors. 16,17 Erlotinib is an orally active, quinazoline TK inhibitor that specifically targets EGFR. The BR.21 phase III study compared Erlotinib versus placebo in patients with stage IIIB/IV NSCLC and one or two prior chemotherapy regimens, and provided the first evidence that EGFR inhibitors extend survival in chemotherapy-refractory NSCLC; patients receiving Erlotinib displayed significant longer overall survival (6.7 versus 4.7 months) and progression-free survival (PFS) (2.2 versus 1.8 months) than those receiving placebo, with an overall RR of 8.9%. In addition, a higher RR was observed among specific subpopulations, including women, Asian ethnicity, patients who had never smoked, and patients with adenocarcinoma.<sup>12</sup> Moreover, expression of EGFR by immunohistochemistry or fluorescent in situ hybridization is another independent predictor of response and survival. 18 We conducted a prospective study to identify prognosis-associated predictive factors in patients treated with Erlotinib in Mexican population.

#### **MATERIALS AND METHODS**

#### **Patient Selection**

With previous approval by the Institutional and Federal Health Office Boards (Instituto Nacional de Cancerología and Secretaría de Salud, Mexico, respectively), we enrolled consecutive unselected patients with advanced NSCLC participating in the TRUST study, an open label, nonrandomized trial initiated to provide erlotinib access to patients with advanced NSCLC, between August 2005 and March 2007. One hundred and fifty patients were included from two national reference centers (Instituto Nacional de Cancerologia and Instituto Nacional de Enfermedades Respiratorias), which take care of patients mainly from rural areas of all the country. All patients gave written informed consent. A com-

plete medical history and physical examination including skin assessment, complete blood count with differential and platelet count, biochemical profile, urinalysis, electrocardiogram, and computed tomography of chest and abdomen were obtained. Details of WSE, including hours per day and years of exposure, were also recorded. WSE was defined as being exposed to fumes resulting from burning of wood in fireplaces and wood stoves for >5 years for at least 4 hours per day.<sup>4</sup> We defined the term non smoker to refer to an individual who has had a lifetime exposure of less than 100 cigarettes.<sup>19</sup>

Eligible patients met the following criteria: histologically or cytologically proven stage IIIB/IV NSCLC; Eastern Cooperative Oncology Group (ECOG) performance status 0 to 3; progression to one or two prior chemotherapy regimens or being considered unsuitable to receive standard chemotherapy or radiotherapy; age  $\geq$ 18 years; ability to swallow tablets; adequate laboratory measurements (WBC  $\geq$ 1,500/mm³, hemoglobin  $\geq$ 10.0 g/dl, platelet count  $\geq$ 100,000/mm³, total bilirubin  $\leq$ 1.5 mg/dl, aspartate aminotransferase  $\leq$ 2.0 mg/dl upper limit of normal; creatinine  $\leq$ 1.5 mg/dl); for females in childbearing age, negative pregnancy test within 72 hours of enrollment; measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), and life expectancy of  $\geq$ 12 weeks.

Patients with known central nervous system metastases were eligible provided that at least 2 months had elapsed since completion of radiation therapy. Patients with prior treatment with any EGFR-targeted agent, major surgery or radiation therapy within the last 21 days, any active gastrointestinal disorder that alters motility or absorption, and severe and unstable medical comorbidities were ineligible.

#### Treatment Plan

Erlotinib was administered within 2 days after screening in an open-labeled fashion to all patients. Patients had to have recovered from any toxic effect of previous treatments and at least 21 days had passed after any previous chemotherapy regimen. All patients received an initial dose of 150 mg per day; each cycle had a duration of 4 weeks. Physical examination and hematologic and biochemical testing were performed in every cycle. Response assessment was performed after every two protocol-treatment cycles according to RECIST criteria. National Cancer Institute Common Toxicity Criteria version 3.0 was used to evaluate toxicity. Dose modifications were made for grade 3 toxicities, restarting at a reduced dose (100 mg/d) if toxicities improved to grade  $\leq 2$ within 14 days. Treatment continued until disease progression, severe or intolerable toxicity, or withdrawal of consent occurred.

## **Statistical Analysis**

Our primary end point was PFS and the secondary end point was overall response. WSE analysis was not preplanned but was considered within the TRUST study. For descriptive purposes, continuous variables were summarized as arithmetic means, medians, and standard deviations, and categorical variables comprised proportions with 95% confidence intervals (95% CI). Inferential comparisons were carried out by Student's *t* or Mann-Whitney *U* test according to distri-

bution of the data (normal and non-normal) determined by the Kolmogorov-Smirnov test.  $\chi^2$  or Fisher exact test was used to assess significance among categorical variables.

Statistical significance was determined as p < 0.05 with a two-sided test. Statistically significant and borderline significant variables (p < 0.1) were included in multivariate logistic regression analysis. PFS was measured from day of enrollment to the date of last follow-up visit and analyzed with the Kaplan-Meier technique, whereas comparisons among subgroups were carried out with the log-rank test. For analysis of survival curves, all variables were dichotomized.

Adjustment for potential confounders was effected by multivariate regression analysis. SPSS software package version 15 (SPSS, Inc., Chicago, IL) was employed for data analysis.

### **RESULTS**

#### **Patients**

A total of 150 patients were included in the study. Clinical characteristics are summarized in Table 1. Median age was  $64 \pm 12$  years. Adenocarcinoma was observed in 71%. Tobacco use was reported by 52.3% of patients and 28.2% had WSE with a median exposition of  $40 \pm 22$  years (4 h/d). Fourteen percent with smoking history had also WSE and 45% of the non smokers presented WSE. All the patients except one (caucasic of French nationality) were hispanics. None of our patients was of Asian origin.

# Response

Response was observed in 51 patients (33.8%; 95% CI, 29.9–37.6) according to RECIST criteria (4.3% complete responses, and 29.5%, partial responses). Stable disease was achieved in 50 patients (33.3%), and 49 patients (32.6%) showed progressive disease. Overall response and stable disease was 67.1%. Clinical subjective improvement and favorable changes in performance status were observed in 56 and 34% of patients, respectively.

Patients who showed response had greater symptomatic relief (95.6 versus 35.9%). Table 2 summarizes response analysis according to clinical and pathologic characteristics. Factors associated with response to Erlotinib in univariate analysis included female gender (45 versus 20%; p=0.002), lack of tobacco use (50 versus 19%; p<0.001), adenocarcinoma (35 versus 20%; p=0.085), and WSE (83 versus 13%; p<0.001). Only the histologic type (p=0.05) and WSE (p<0.001) were of statistical significance in the logistic regression analysis.

#### **Progression-free Survival**

All patients were included in the PFS analysis. Median follow-up was 4.5 months and median PFS was 7.6 months (95% CI, 5.3–9.7). PFS-associated clinical and pathologic characteristics are summarized in Table 3. Factors associated with longer PFS in univariate analysis comprised adenocarcinoma (7.9  $\pm$  0.8 versus 2.3  $\pm$  0.4 months; p = 0.001), female gender (8.4  $\pm$  0.73 versus 5.3  $\pm$  0.96 months; p = 0.025), tobacco use (12.7  $\pm$  2.9 versus 4.9  $\pm$  0.77 months; p = 0.002), ECOG performance status (8.9  $\pm$  2.9 versus

**TABLE 1.** Baseline Patient Characteristics

Characteristic	No. of patients	%
Patients enrolled	150	
Gender		
Male	70	47
Female	80	53
Age, yr		
Median ± SD		$62.4 \pm 12.2$
Range		33-88
<65	87	57.7
≥65	63	42.3
ECOG PS		
0	10	6.6
1	50	33.3
2	43	28.6
3	47	31.3
Stage at enrollment		
IIIB	28	18.4
IV	122	81.6
Histology		
Adenocarcinoma	107	71
Other NSCLC	43	29
Smoking status		
Non-smokers	72	47.7
Ever-smokers	78	52.3
CNS metastases		
Presence	30	20.1
Absence	120	79.9
WSE		
Median ± SD		$40 \pm 22$
Presence	42	28.2
Absence	108	71.8
Lines of treatment		
First	50	33.3
Second	78	52.2
Third	22	14.5

WSE, wood-smoke exposure; CNS, central nervous system; PS, performance status.

6.5  $\pm$  1.4 months; p=0.058), and WSE (17.6  $\pm$  1.1 versus 5.3  $\pm$  0.9 months; p=0.001). However, in multivariate analysis only adenocarcinoma (p=0.009) (Figure 1*A*), female gender (p=0.04) (Figure 1*B*), and WSE (p=0.006) (Figure 1*C*) showed statistical significance. The median survival was of 12.4  $\pm$  2.9 months with a 1-year overall survival of 50% (95% CI, 41–59) and 18.4% at 2 years (95% CI, 41–59). WSE patients had a longer overall survival (19.2  $\pm$  1.3 months) compared with those with no WSE (7.7  $\pm$  1.2) (p<0.001).

#### **Toxicity**

There were no Erlotinib-related deaths. The most frequent toxicity was rash in 75% of the patients; nevertheless only 15% presented grade 3 and 4, which required dose reduction or treatment withdrawal (5%). Grade 1 and 2 diarrhea was present in 30% of the patients.

**TABLE 2.** Relationship Between Clinical Variables and Antitumor Response in Patients Treated with Erlotinib

Factor	No. of Responses (complete and partial)	Overall Response Rate (%)	Univariate Hazard Ratio (95% CI)	p	Multivariate Hazard Ratio (95% CI)	p
Gender			3.2 (1.5–6.9)	0.002	3.6 (0.7–18)	0.12
Male	15	20.0				
Female	36	45.0				
Age			1.3 (0.65-2.7)	0.45		
<65 yr	27	31.0				
≥65 yr	24	38.0				
ECOG PS			1.5 (0.7–3.1)	0.32		
0-1	17	28.3				
2–3	34	37.7				
Stage at enrollment			1.6 (0.56-4.8)	0.36		
IIIB	7	25.0				
IV	44	36.0				
Histology			2.7 (0.84-8.9)	0.085	4.8 (1–26)	0.05
Adenocarcinoma	38	35.5				
Other NSCLC	9	20.0				
Smoking status			4.02 (1.9-8.6)	< 0.001	1.2 (0.3-5.1)	0.8
Non-smokers	36	50.0				
Ever-smokers	15	19.2				
CNS metastases			0.9 (0.38-2.2)	0.83		
Presence	10	33.3				
Absence	41	34.0				
WSE			35.4 (12.87–97.4)	< 0.001	38.1 (9.7–149.7)	< 0.001
Presence	35	83.3				
Absence	14	13.3				
Lines of treatment			1.1 (0.5–2.5)	0.75		
First	16	32.0				
Second/Third	35	35.0				

WSE, wood-smoke exposure; CNS, central nervous system; PS, performance status.

#### DISCUSSION

In the present study, we found an overall response in 33.8% of patients with NSCLC treated with Erlotinib. This rate is higher than the documented by other groups who treated unselected patients with advanced NSCLC with Erlotinib. 12,20,21 In the interim analysis of compassional use of Erlotinib, a total of 5908 patients were included.<sup>22</sup> Overall response was reported in 10% of patients with median PFS of 15.1 week, with 12.4 weeks after first-line and 12.7 weeks after second line chemotherapy. 18 This finding suggests that the clinical characteristics of our cohort are different when compared with those of previous studies. In our population, the smoking history was reported in 53%, which is lesser to that reported in developed countries. However, epidemiologic studies of NSCLC in Mexico have shown a 66% of smokingassociated lung cancer.<sup>23</sup> It is important to mention that patients included in this study were not selected based on their clinical characteristics, but mainly on their assistance to the pulmonary neoplasms clinic of the hospitals previously mentioned. These differences could be associated with a higher overall response. In univariate analysis, we found similar response predictive factors to those previously reported, such as female gender, adenocarcinoma, and lack of

tobacco use.<sup>24–30</sup> Nonetheless, after adjusting for gender, ECOG status, and histologic type we found that the most important independent factor associated to both longer survival and response was WSE, with an overall response of 83.3% and PFS of 17.6 months. In addition, in the absence of WSE we found response and PFS rates (12.3% and 5.3 months, respectively) similar to what had been previously reported. 12,20,21 It is known that WSE is a risk factor for lung cancer.31 However, few studies consider this factor in subgroup analysis, owing the fact that nearly all studies are performed in developed countries, in which WSE is unusual. However, our cohort included a high percentage of people living in rural areas and we found that 28% of patients had WSE-related NSCLC. In our cohort, the lack of association in the multivariate analysis of clinical-pathologic factors previously described in the literature for response and PFS could be consequence of a strong association between the endpoints and WSE. The finding that WSE is the most important independent predictor of PFS and response to Erlotinib treatment has not been previously reported.

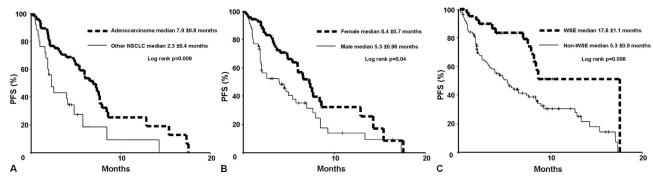
The most prominent predictor of somatic mutations in EGFR is lack of cigarette smoking.<sup>32,33</sup> When considering all geographic and ethnic groups, EGFR mutations are identified

Factor			Multivariate Analysis		
	Median ± SE	Univariate Analysis (p)	Hazard Ratio	95% CI	p
Sex		0.025	0.54	0.3-0.97	0.04
Male	$5.3 \pm 0.96$				
Female	$8.4 \pm 0.73$				
Age		0.62			
<65 yr	$7.6 \pm 1.6$				
≥65 yr	$7.4 \pm 1.4$				
ECOG PS		0.058	1.6	0.9 - 2.9	0.106
0-1	$8.9 \pm 2.9$				
2–3	$6.5 \pm 1.4$				
Stage at enrollment		0.77			
IIIB	$8.4 \pm 2.7$				
IV	$7.0 \pm 1.2$				
Histology		0.001	0.45	0.25-0.81	0.009
Adenocarcinoma	$7.9 \pm 0.8$				
Other NSCLC	$2.3 \pm 0.4$				
Smoking status		0.002	1.05	0.5 - 2.02	0.871
Non-smokers	$12.7 \pm 2.9$				
Ever-smokers	$4.9 \pm 0.77$				
CNS metastases		0.58			
Presence	$7.3 \pm 1.6$				
Absence	$6.6 \pm 1.2$				
WSE		0.001	0.36	0.18 – 0.75	0.006
Presence	$17.6 \pm 1.11$				
Absence	$5.3 \pm 0.9$				
Lines of treatment		0.63			
First	$5.3 \pm 1.7$				
Second/third	$7.6 \pm 0.9$				
WSE, wood-smoke e	xposure; CNS, central ne	ervous system; PS, performance statu	ıs.		

in 51% of never smokers versus 10% of ever smokers.<sup>33,34</sup> Preliminary data have suggested that patients with lung cancer with tumors displaying EGFR-TK domain mutations respond better to Erlotinib than those without such mutations.<sup>34</sup> In addition, K-Ras mutations are reported to occur in 30 to 50% of patients with tobacco-associated adenocarcinoma of lung,<sup>31</sup> and K-Ras mutation is associated with lack of response to Erlotinib.<sup>18</sup> These data strongly support the no-

tion that lung tumorigenesis proceeds through different molecular mechanisms according to smoking status.<sup>35</sup> Current evidence indicates that lung cancer in never smokers or lung cancer associated with other risk factors such as WSE constitute a distinct disease entity with unique molecular and biologic characteristics.

It is known that there are significant changes in Erlotinib pharmacokinetic in smokers compared with non smok-



**FIGURE 1.** Kaplan-Meir plots of PFS for patients receiving Erlotinib treatment classified according to (*A*) histology, (*B*) gender, and (*C*) WSE status.

ers with a significant decrease in area under the curve, possibly because of an induction of cytochrome P450 (CYP3A4 and CYP3A5).<sup>36,37</sup> Nevertheless, there is no information about differences in clearance of Erlotinib or Gefitinib. WSE in contrast to cigarette smoking does not induce the activity or expression of cytochromes at pulmonary level in rats.<sup>38</sup> So it is unlikely that WSE could affect Erlotinib clearance and explain our results.

In relation to central nervous system metastasis, there have been reports about response to Erlotinib treatment when EGFR mutation is present, which suggest that inhibitors of EGF-receptor TK are capable of penetrating the blood–brain barrier in presence of cerebral metastasis. This could explain the absence of poor prognosis related with cerebral metastasis when patients were treated with Erlotinib.<sup>39,40</sup>

Limited data are available on the etiopathogenesis, molecular abnormalities, and prognosis of WSE-related NSCLC; nevertheless, the association between WSE and better response and PFS suggests that carcinogenic mechanisms in NSCLC involve EGFR and/or absent K-Ras mutations. Molecular studies in signaling pathways related with EGFR and K-Ras in patients with WSE-associated NSCLC are warranted. In conclusion, patients with WSE-related NSCLC have a high probability of response to Erlotinib with a higher PFS.

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