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ORIGINAL ARTICLE

Prognostic factors for patients with advanced non-small cell lung cancer treated with gemcitabine-platinum as first-line therapy in an observational setting in China

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Abstract

Background: This study examined the prognostic factors associated with survival in advanced non-small cell lung cancer (NSCLC) patients receiving gemcitabine-platinum regimens as first-line therapy in real-world clinical settings in China.

Methods: Data was analyzed from a multinational, prospective, non-interventional, observational study of individuals receiving gemcitabine-platinum regimens as first-line therapy for NSCLC, focusing on 300 patients from mainland China. A Cox regression model was used to determine the association of 38 prognostic factors, including patient smoking characteristics, with overall survival.

Results: In these 300 patients, the mean age was 58.9 (±10.8) years, with males comprising 71% of the population. Thirty percent of patients had an Eastern Cooperative Oncology Group performance status (PS) of 0 and 70% had a PS of 1. The majority of patients had NSCLC of adenocarcinoma origin (57%). Multivariate Cox regression analyses adjusted for baseline factors revealed that gender, tumor (T) staging, metastasis (M) staging, liver metastases, serum albumin, and superior vena cava obstruction were significant prognostic factors. Smoking during therapy was not significantly associated with survival, although numbers were small for this variable ($n = 16$). Weight loss of >10% was a significant prognostic factor for adverse events.

Conclusions: Gender, T staging, M staging, liver metastases, superior vena cava obstruction, and serum albumin are prognostic factors affecting overall survival in mainland Chinese patients receiving first-line gemcitabine-platinum regimens for advanced NSCLC. These negative prognostic factors may warrant further investigation in clinical trials.

Introduction

Non-small cell lung cancer (NSCLC) is a burgeoning problem in China.[1] In 2012, approximately 653 000 people were newly diagnosed with lung cancer and 597 000 people died from the disease.[2] In China, the most common first-line regimen for patients with late stage (stage IIIB-IV) NSCLC is gemcitabine with either carboplatin or cisplatin.[3] Given the common use of gemcitabine-platinum combinations, it is important to evaluate prognostic factors associated with clinical outcomes, as well as current use and treatment patterns in normal practice, to better realize the benefits of prognostic factors in the treatment of NSCLC patients in China.

Many prognostic factors are associated with outcomes in NSCLC, including disease stage, performance status, age, weight loss, gender, and smoking.[4,5] We have previously examined prognostic factors, including smoking, in patients receiving gemcitabine-platinum therapy for advanced NSCLC in nine countries, including China, in a single-arm, prospective, non-interventional, observational study.[6] In geographically distinct populations, there are differences in a variety of factors that affect outcome and response to treatment, including clinical practice, access to care, and overall genetic variation.[7,8] To better understand the prognostic factors that may affect outcomes in Chinese populations, we analyzed data for a subset of mainland Chinese patients from

the larger observational study.[6] The objective of this study was to use multivariate Cox regression modeling adjusted for patient baseline factors to determine the role of previously identified prognostic factors, including smoking during therapy, on overall survival (OS) and adverse event (AE) profiles in Chinese patients receiving a gemcitabine-platinum regimen as first-line chemotherapy for treatment of advanced NSCLC.

Methods

Data source

This was a prospective, non-interventional, observational study that enrolled 300 patients at 40 clinical sites in mainland China as part of a larger (n = 1214), nine-country study (B9E-AA-B004) previously reported.[6] Gemcitabine-platinum treatment for the Chinese patients in this study started between 2004 and 2005 and ended between 2004 and 2006. The overall study, as well as this subanalysis, was designed to assess the effect of prognostic factors, including continued smoking during therapy, on treatment outcomes in patients receiving a gemcitabine-platinum regimen as first-line therapy for treatment of advanced NSCLC. Regulatory and ethics requirements were followed for all countries involved in the study, including China. Written informed consent was obtained from all participants prior to enrolment. All care was provided at the discretion of the treating physician to reflect the routine clinical setting (this included visit frequency, advice regarding smoking behavior, and procedures performed at visits). Patients were followed for survival until death or until 18 months after the start of their gemcitabine-platinum therapy. All patients who received at least one dose of gemcitabine-platinum therapy were included in efficacy and safety analyses unless otherwise noted.

Measures

Many of the prognostic factors analyzed in this study were previously identified as prognostic factors associated with outcomes in NSCLC.[4] A total of 38 prognostic factors were examined, including: continued smoking during therapy; number of cigarettes/day during therapy; baseline smoking level; continuing smoker versus ex-smoker; heavy smoker at baseline; never smoked; disease stage; hypercalcemia; tumor node metastasis staging (T, N, and M); weight loss of >10%; Eastern Cooperative Oncology Group (ECOG) performance status; superior vena cava obstruction present; age <70 years; gemcitabine-platinum regimen; largest tumor >5 cm; gender; metastatic disease (extra-thoracic, liver, bone, brain); diagnosis (histology); dyspnea present; cough present; hemoptysis present; pain present; expectoration present; chronic obstructive pulmonary disease present; pleural effusion present; albumin (normal range indicator); hemoglobin; aspartate aminotransferase; alanine aminotransferase; bilirubin (total); albumin; lactate dehydrogenase; and calcium.

Statistical methods

Kaplan-Meier survival analysis was used to assess OS (time to death). Survival time was calculated from the start of gemcitabine-platinum therapy to the date of death as a result of any cause. Patients who were lost to follow-up or who were alive at the completion of the study were treated as censored. Univariate Cox regression analysis was used to assess the association between each variable and OS.

A multivariate regression Cox model was built, similar to that reported by Li *et al.*[6] A stepwise Cox regression (with entry and stay cutoff levels of 0.1) was performed using all variables (excluding smoking variables) with <10% missing values. Key prognostic factors identified by Brundage *et al.*[5] were forced into the model. These factors were disease stage, hypercalcemia, "N" factor, weight reduction, performance status, and superior vena cava obstruction. Results from Cox regression analyses are reported as hazard ratios (HRs) with 95% confidence intervals (CIs) and P-values.

To identify the association between occurrence of AEs and the baseline factors, univariate and multivariate logistic regression models were used. All analyses were performed using the SAS program (Version 9.2, SAS Institute; Cary, NC) with a two-sided alpha of 0.05.

Results

Participant characteristics and treatments

Baseline demographics and clinical characteristics are presented in Table 1. Patients (n = 300) were all mainland Chinese and had a mean (±standard deviation) age of 58.9 (±10.8) years, with males comprising 71% of the population. Epidermal growth factor receptor (EGFR) mutation status was not available for patients because EGFR mutation analysis was not routine clinical practice at the time of this study.

Overall, 58.7% of patients had smoked at some point prior to therapy (i.e. ever smokers). Smoking characteristics of patients are shown in Table S1. Nearly two-thirds of ever smokers (64.6%) had ceased smoking at the initiation of therapy or within six months prior to treatment commencement, whereas 5.3% of smokers continued to smoke during therapy. Of those patients continuing to smoke during therapy, the mean number of cigarettes smoked per day was 13.2 (95% CI: 7.95, 18.4).

The majority of patients had NSCLC of adenocarcinoma origin (57%). Sixty percent of patients were assigned to gemcitabine-cisplatin treatment, and 40% were assigned to

Table 1 Baseline characteristics

Variable	(*N* = 300)
Age, years, mean ± standard deviation	58.9 ± 10.8
Performance status (ECOG), *n* (%)	
0	89 (29.7)
1	211 (70.3)
Gender, *n* (%)	
Female	87 (29.0)
Male	213 (71.0)
Tumor stage, *n* (%)	
Stage IIIB	134 (44.8)
Stage IV	165 (55.2)
Brain metastasis, *n* (%)	
No	286 (95.3)
Yes	14 (4.7)
Tumor type, *n* (%)	
Adenocarcinoma	171 (57.0)
Squamous cell carcinoma of lung	89 (29.7)
Mixed cell carcinoma of lung	11 (3.7)
Large cell lung carcinoma	3 (1.0)
Non-small cell carcinoma NOS	26 (8.7)
Hypercalcemia (calcium >2.75 mmol/L), *n* (%)	
Yes	4 (1.5)
No	255 (98.5)
Weight loss >10% during the last 6 months, *n* (%)	
Yes	50 (16.9)
No	245 (83.1)
Superior vena caval obstruction at start of therapy, *n* (%)	
Yes	5 (1.7)
No	288 (98.3)
Chronic obstructive pulmonary disease at start of therapy, *n* (%)	
Yes	26 (8.8)
No	271 (91.2)
Prescribed NSCLC treatment, *n* (%)	
Gemcitabine-carboplatin	120 (40.0)
Gemcitabine-cisplatin	180 (60.0)

ECOG, Eastern Cooperative Oncology Group; *N*, total number of patients; *n*, number of patients in specified category; NOS, not otherwise specified; NSCLC, non-small cell lung cancer.

gemcitabine-carboplatin. The mean number of gemcitabine-platinum cycles received was 3.13 (95% CI: 2.98–3.27), with 26% of patients receiving no therapy post gemcitabine-platinum treatment. The most common second-line treatments were docetaxel (19.7%) and radiotherapy (14.3%). Of the 300 patients enrolled, 69 (23%) were alive at study completion, 154 (51.3%) had died, and 77 (25.7%) were lost to follow-up.

Efficacy and toxicity of gemcitabine-platinum treatment

Median OS time (Fig 1) was 15.6 months (95% CI: 12.5–17.4). Most of the deaths on the study were the result of the study disease (153/154, 99.4%). A total of 94 patients (31.3%) completed the study treatment; 63 patients (21%) discontinued treatment after experiencing an adequate response, 77 patients (25.7%) discontinued because of inadequate response, 40 patients (13.3%) discontinued at their discretion, and seven patients (2.3%) died while on study treatment. Noncompliance was reported as the reason for treatment discontinuation in nine patients (3%). Ten patients (3.3%) discontinued study therapy because of an AE, and 74 patients (24.7%) experienced at least one AE. The most frequently reported AEs were low hemoglobin count (<8.0 g/dL; $n = 41$, 13.7%), thrombocytopenia (<50.0×10^9/L with bleeding; $n = 35$, 11.7%), and low neutrophil count (<1.0×10^9/L associated with fever of ≥38.5°C or documented infection; $n = 16$, 5.3%) (Table 2).

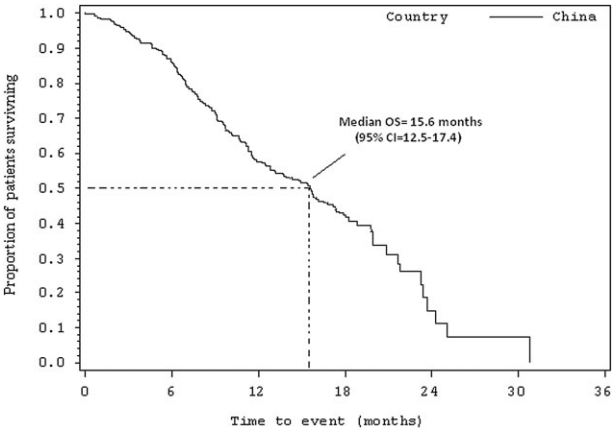

Figure 1 Kaplan-Meier overall survival in Chinese patients with advanced non-small cell lung cancer (NSCLC). CI, confidence interval; OS, overall survival.

Table 2 Adverse event rates as a proportion of patients

Variable	Total (*N* = 300) *n* (%)	(95% CI)
Missing	7 (2.3)	(0.9, 4.7)
At least one event	74 (24.7)	(19.9, 29.9)
Absolute neutrophil count of <1.0×10^9/L associated with fever of >38.5°C or documented infection	16 (5.3)	(3.1, 8.5)
Thrombocytopenia <50.0×10^9/L with bleeding	35 (11.7)	(8.3, 15.9)
Hemoglobin <8.0 g/dL (or <80 g/L or <4.9 mmol/L)	41 (13.7)	(10.0, 18.1)
Documented infection requiring hospitalization or intravenous antibiotics	11 (3.7)	(1.8, 6.5)
Life-threatening toxicity	1 (0.3)	(0.0, 1.8)
None	219 (73.0)	(67.6, 77.9)

CI, confidence interval; *N*, total number of patients; *n*, number of patients in specified category.

Table 3 Unadjusted univariate analyses of prognostic factors† using Cox proportional hazard modelling

Variables in the model	Hazard ratio	Lcl for HR	Ucl for HR	*P*-value
Age <70 years versus ≥70 years	1.18	0.788	1.78	0.416
Gender	0.826	0.577	1.18	0.297
Performance status	1.46	1.01	2.10	**0.044**
TNM staging (T)				0.064
T2 versus T1	4.12	1.49	11.4	**0.007**
T3 versus T1	5.52	1.87	16.3	**0.002**
T4 versus T1	4.58	1.66	12.6	**0.003**
Tx versus T1	6.54	1.45	29.5	**0.015**
Dyspnea present	1.48	1.06	2.07	**0.022**
Cough present	1.67	1.14	2.44	**0.009**
Expectoration present	1.59	1.15	2.19	**0.005**
Chronic obstructive pulmonary disease present	1.85	1.12	3.08	**0.017**
Metastatic disease-liver	1.59	0.968	2.60	0.067
Continued smoking during therapy	1.11	0.566	2.19	0.755
Number of cigarettes/day during therapy	0.999	0.955	1.04	0.955
Baseline smoking level (pack-years)	0.999	0.994	1.01	0.754
Continuing smoker versus ex-smoker	1.09	0.544	2.18	0.811
Heavy smoker at baseline	1.05	0.744	1.47	0.797
Never smoked	1.08	0.779	1.50	0.648

†Selected factors for demographics, statistically significant prognostic factors, and smoking behavior. HR, hazard ratio; Lcl, lower confidence limit; Ucl, upper confidence limit; TNM, tumor node metastasis.

Univariate analysis of prognostic factors for survival

Of 38 prognostic factors analyzed, six were found by univariate Cox regression analysis to be significantly ($P < 0.05$) associated with survival, and these were ECOG performance status, T staging, dyspnea, cough, expectoration, and chronic obstructive pulmonary disease (Table 3).

Multivariate regression analysis of prognostic factors for survival

HRs and 95% CIs from the multivariate Cox regression analysis of prognostic factors are illustrated by forest plot in Figure 2. Prognostic factors of T staging, M staging, gender, metastatic disease in the liver, superior vena cava obstruction, and serum albumin were identified as significant ($P < 0.05$). The smoking variables added to the established model did not reach significance.

Analysis of factors associated with adverse events

Logistic regression of AEs after stepwise selection with gender included in the model revealed weight loss >10% to be a significant predictor of AEs (odds ratio = 0.41, 95% CI: 0.17–0.97, $P < 0.05$). After adding the smoking variables into the model, ever smoking and continued smoking were not significant in this logistic regression.

Discussion

NSCLC is estimated to claim nearly 1.4 million lives around the world annually,[8] and is the leading cause of cancer death in China.[2] Geographic and ethnic differences in cancer incidence and prognosis are increasingly being recognized.[9–11] For example, in the United States, approximately 45% of NSCLC patients are women, whereas in Eastern Asia, only 25–30% of NSCLC patients are female.[10,12] In Chinese populations, different prognostic factors have been, and are continuing to be identified that may affect patient therapy and future clinical trials in these populations and geographies.[11,12]

The current analysis examined the impact of smoking and other prognostic factors in the Chinese subset of patients from a large multi-country, prospective, non-interventional, observational study investigating survival and other treatment outcomes with gemcitabine-platinum chemotherapy.[6] Prognostic factors in the Chinese subgroup that were significantly associated with decreased OS were male gender, T stage >1, M stage (presence of any metastasis), liver metastases, elevated serum albumin, and superior vena cava obstruction. In addition, expectoration and chronic obstructive pulmonary disease were identified as significant prognostic factors by univariate analysis in the mainland Chinese population that were not identified in the larger overall study population.

The prognostic factors identified in the mainland Chinese population differed from those observed in the broader nine-country overall study population from which the Chinese population was derived. For instance, while the specific

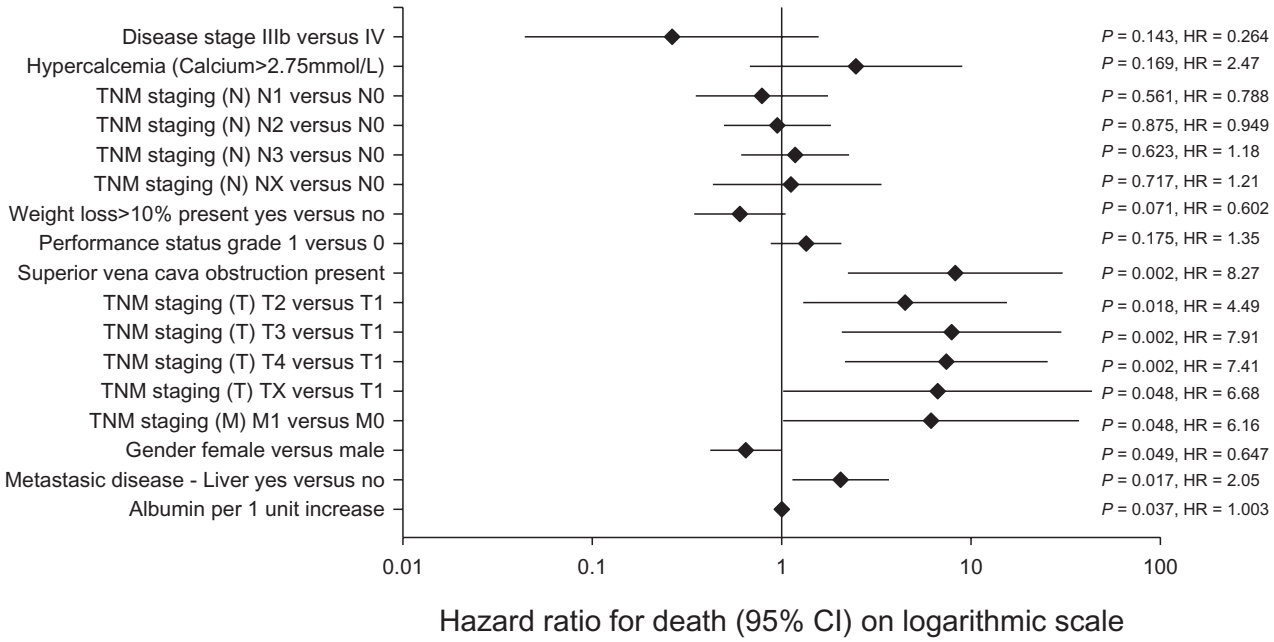

Figure 2 Prognostic factors associated with survival in non-small cell lung cancer (NSCLC) of a Chinese patient subgroup (multivariate Cox regression model). CI, confidence interval; HR, hazard ratio.

platinum agent used in combination with gemcitabine was a significant prognostic factor in the overall study, mainland Chinese patients in this study did not have a survival difference based on cisplatin or carboplatin selection in combination with gemcitabine. This may reflect the smaller subset population under study or could be related to some as yet undetermined genetic variation that influences platinum sensitivity in the Chinese population somewhat differently than other populations. Furthermore, whereas ECOG performance status and T stage were prognostic factors for survival in both analyses, dyspnea, cough, and chronic obstructive pulmonary disease were significantly associated with poorer OS only in the Chinese mainland population, and were not significant predictors in the overall trial population (n = 1214), which comprised eight other countries including Taiwan (n = 195). Dyspnea, cough, and chronic obstructive pulmonary disease, in addition to smoking, may be associated with increased levels of air pollution in large population centers in China.[13]

Weight loss of >10% was the only prognostic factor associated with the incidence of AEs in the Chinese population, whereas the entire nine-country study population identified five prognostic factors that were associated with the incidence of AEs (i.e. disease stage [IIIB vs. IV], country, weight loss of >10%, age <70 years, and the presence of pain). The difference in the results of the Chinese population may reflect that the current analysis lacked the scope to readily detect such associations, but may also reflect biological differences between these different populations.

The current analysis has several limitations, including the fact that the overarching study was observational, which can be subject to bias and potential confounding. Furthermore, as all of the measurements of effectiveness were subjective, they were not of sufficient scientific rigor to be analyzed as prognostic factors. The relatively small patient subgroup analyzed (n = 300) is another limitation, although this may represent one of the largest analyses to date of Chinese patients receiving chemotherapy for NSCLC in a real-world setting.

Conclusion

In summary, for mainland Chinese patients with advanced NSCLC receiving first-line gemcitabine-platinum doublet therapy in a real-world setting, prognostic factors differed from those found in the larger overall nine-country dataset. Smoking while on therapy did not appear to be a negative prognostic factor for these patients; however, the number of patients continuing to smoke during chemotherapy was small overall, and somewhat less than has been reported in other recent trials in NSCLC. This may reflect the growing effectiveness of smoking cessation programs and greater overall awareness of the link between smoking and lung cancer in China. Male gender, T stage >1, M stage (presence of any metastasis), liver metastases, elevated serum albumin, and superior vena cava obstruction may be poor prognostic factors in mainland Chinese NSCLC patients treated in a real-world setting. These prognostic factors should be considered in future clinical trials of gemcitabine-platinum therapy in this population.

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Disclosure

WY, ZK, NR, YY, and JW are employees of Eli Lilly and Company. SQ has no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Smoking characteristics at baseline and during study.

