Treatment strategy, overall survival and associated risk factors among patients with unresectable stage IIIB/IV non-small cell lung cancer in China (2015–2017): A multicentre prospective study

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Summary

Background There are limited studies on treatment and survival analysis among patients with unresectable Stage IIIB or IV non-small cell lung cancer (NSCLC) in routine practice in China. To address this gap, we conducted a prospective observational study in a cohort of patients treated at 11 hospitals in China.

Methods This was a multicentre, prospective cohort study including patients with newly diagnosed unresectable Stage IIIB or IV NSCLC from June 26th, 2015 to April 28th, 2017. Patient baseline characteristics, disease characteristics, and anti-cancer treatments were obtained by medical chart review. The overall survival (OS) from the initiation of first-line treatment was analysed by the Kaplan-Meier method. Factors associated with survival were analysed by univariate and multivariate Cox regression models.

Findings Among 1324 patients enrolled with median follow-up duration of 15·0 (range: 0·0–42·1) months, 83·5% (1105/1324) of them received first-line chemotherapy of which platinum-based compounds were the dominated agents. Overall, 30·9% (409/1324) of patients received targeted therapy as 1st-line treatment including 65·0% (266/409) EGFR-TKIs and 5·1% (21/409) ALK-TKIs. Of all eligible patients, gene testing rates were 44·0% (583/1324) for *EGFR* mutations, 17·0% (225/1324) for *EML4-ALK* gene fusions, and 8·3% (110/1324) for *ROS1* gene fusions. The EGFR-TKIs were administered to 63·9% (179/280) of *EGFR* mutated patients as first-line treatment. The overall median OS was 23·2 (95%CI 19·5-25·5) months, and patients treated at tier 1 cities had better OS than that of tier 2 cities. Also, the OS in patients with *EGFR* mutation was longer than those with *EGFR* wild type. Multivariate Cox regression models suggested that male, education below high school, tier 2 cities, smoking history, and multiple metastases were associated with poor survival.

Interpretation The gene test coverage was relatively low among the studied population, and over half of *EGFR* mutated patients received EGFR-TKIs, suggesting that the result of genetic tests in real-world settings may not always indicate the selection of treatment. The OS benefit observed from patients treated in tier 1 cities and those

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with *EGFR* mutation may indicate a need for broader gene test coverage, providing NSCLC patients with personalized treatment according to the results of genetic tests.

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TRANSLATED ABSTRACT: This translation in Chinese was submitted by the authors and we reproduce it as supplied. It has not been peer reviewed. Our editorial processes have only been applied to the original abstract in English, which should serve as reference for this manuscript.

摘要

背景介绍:

目前针对中国不可切除的IIIB期或IV期非小细胞肺癌(NSCLC)患者在临床实践中的治疗模式和生存分析的研究有限.为了填补这一空白,我们开展了一项前瞻性,观察性研究,纳入来自11家医院的患者.

方法:

这是一项多中心,前瞻性队列研究, 纳入了2015年6月26日至2017年4月28日新诊断为不可切除的IIIB期或IV期NSCLC患者.通过病历筛查获得基线特征,临床肿瘤特征和抗肿瘤治疗.采用Kaplan-Meier法分析从开始一线治疗后的总生存期(OS),并通过单因素和多因素Cox回归模型分析与生存相关的影响因素.

结果:

在入组的1324例患者中,中位随访时间为15.0个月(范围:0.0-42.1),其中83.5%(1105/1324)的患者接受了一线化疗,以铂类化合物为主.总体而言, 30.9%(409/1324)的患者接受靶向治疗作为一线治疗, 其中包括65.0%(266/409)的患者接受了EGFR-TKI治疗和5.1%(21/409)的患者接受了ALK-TKI治疗.在所有符合条件的患者中, EGFR突变,EML4-ALK基因融合和ROS1基因融合的基因检测率分别为44.0%(583/1324),17.0%(225/1324)和8.3%(110/1324).63.9%(179/280)的EGFR突变患者接受EGFR-TKI作为一线治疗.全组患者的中位总生存期为23.2 (95%置信区间 19·5-25·5) 个月,在一线城市治疗的患者的总生存期优于二线城市的患者.此外, EGFR突变患者的总生存期长于EGFR野生型患者.多因素Cox回归模型分析表明, 男性,高中以下文化程度,二线城市,吸烟史及肿瘤转移与较低的生存率相关.

解释:

本研究人群中的基因检测覆盖率相对较低, 其中超过一半的EGFR突变患者接受了EGFR-TKI治疗, 这表明在真实世界诊疗中, 基因检测的结果可能并不完全指导治疗选择.总生存期在一线城市接受治疗的患者和EGFR突变的患者中更佳的现象, 可能提示需要更广泛的基因检测覆盖, 并根据基因检测结果为NSCLC患者提供个体化治疗.

Keywords: Treatment strategy; Overall survival; NSCLC; Risk factors; Prospective study; China

Research in context

Evidence before this study

We searched PubMed website using "NSCLC", "treatment strategy" or "treatment patterns", and "China" as keywords to identify eligible published articles. Several of them focused on economic burden and cost effectiveness of treatments used for non-small cell lung cancer (NSCLC). Several focused on the treatment pattern for specific drug or treatment line used for NSCLC. There was one article which focused on the treatment patterns and outcome of Chinese patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutations. There was another article which focused on one city's treatment pattern for NSCLC patients. We also searched PubMed website using "NSCLC", "risk factor", and "China" as keywords to identify eligible published articles. Most of them focused on specific risk factor or a combination of several risk factors for NSCLC. There were two case-control studies focusing on specific risk factors and their combined effect on NSCLC. However, no previous study prospectively assessed both the treatment strategy, overall survival and associated risk factors for patients with unresectable Stage IIIB or IV NSCLC in China.

Added value of this study

This study is a multicentre, prospective cohort study including patients with newly diagnosed unresectable Stage IIIB or IV NSCLC from June 26th, 2015 to April 28th, 2017. The patients were treated across 11 hospitals in China among different cities. It provides patient baseline characteristics, disease characteristics, and anti-cancer treatment strategies for NSCLC patients. The overall survival and risk factors are also analysed, providing an overall understanding on treatment and survival for unresectable Stage IIIB or IV NSCLC patients in China.

Implications of all the available evidence

From the results of this study, it is observed that the gene test coverage was relatively low among the studied population, with 63·9% of *EGFR* mutated patients receiving EGFR-TKIs. The overall survival benefit was observed from patients treated in tier 1 cities and those with *EGFR* mutation. The study indicates that the result of genetic tests in real-world settings may not always result in the selection of targeted therapy and suggests the possible difference in healthcare resources among tier 1 and tier 2 cities in China for NSCLC patients. Further indication might include a need for broader gene test coverage, providing NSCLC patients with personalized treatment according to the results of genetic tests. Therefore, this study could provide useful information and direction for further investigation and analysis.

Introduction

Lung cancer is the leading cause of cancer-related deaths,[1] and remains a major global unmet medical need, with estimated 2.2 million new diagnoses and 1.8 million deaths worldwide in 2020. Globally, more than half (58%) newly diagnosed patients with lung cancer occurred in developing countries.[1] In China, lung cancer ranks the first among all cancers in terms of incidence and prevalence and is the leading cause of cancer death.[1,2] The most recent national report showed that in 2015, an estimated 83·6% (610,000 of 730,000) of new patients diagnosed with lung cancer died in China.[3]

Among all subtypes of lung cancer, non-small cell lung cancer (NSCLC) is the predominant one, accounting for approximately 85% of all cases.[4] Only about 30% of the new NSCLC patients were diagnosed at the early stage, and the rest (70%) were diagnosed with advanced stage (Stages IIIB or IV).[5]

Chemotherapy is the fundamental treatment option for patients with advanced NSCLC.[6] In addition to chemotherapy, targeted therapy has been developed as a treatment option for patients with gene aberrations as well, and much of the work has been focused on mutations of the epidermal growth factor receptor (*EGFR*), and echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (*EML4-ALK*) fusion oncogene in the last decade.[7] Previous studies also revealed that *EGFR* mutations were substantially more common in Asian-Pacific patients than those in non-Asian patients.[8–11]

Given the high mortality rate as well as the heterogeneity in terms of clinical, pathological, and molecular characteristics, the selection of treatment for patients with advanced NSCLC in routine practice remained challenging.[12,13] Moreover, the real-world treatment patterns among patients with advanced NSCLC have not been fully understood yet in China, and the differences in clinical managements between geographical locations seemed to exist.[14] Notably, the healthcare resource allocation, gene testing rate along with patients' socioeconomic status are imbalanced among different tiers of cities in China, and this heterogeneity may further influence the treatment patterns and clinical outcomes. The *EGFR* testing rate for advanced NSCLC patients in tier 1 cities was reported almost twice higher than that in tier 2 cities (69.0% vs 37.3%).

Therefore, this multicentre, prospective cohort study was conducted to describe disease characteristics and treatment strategy of unresectable Stage IIIB or IV NSCLC patients stratified by the tier level of the city, to estimate the overall survival (OS), and to explore the risk factors associated with mortality.

Methods

Ethics

This study was conducted in accordance with Guidelines for Good Clinical Practices[15] and Guidelines for Good Pharmacoepidemiology Practices,[16] and investigators were trained according to applicable Sponsor Standard Operating Procedures (SOPs). Prior to starting this study, protocol amendments were approved by the Institutional Review Board/Independent Ethics Committee in accordance with local regulatory requirements.

Study design

This was a multicentre, prospective, observational study enrolling patients with newly diagnosed, unresectable Stage IIIB or IV NSCLC from 11 hospitals in China (NCT02458651). Patients were treated and followed up according to their physicians' discretion. All patients were followed up until death, withdrawal of consent, loss to follow-up, or study termination/closure, whichever came first.

Population

Consented patients with a newly diagnosed, unresectable Stage IIIB or IV NSCLC from June 26th, 2015 to April 28th, 2017 were eligible for enrolment if they had not participated in any anti-cancer, treatment-specified clinical trials (detailed inclusion and exclusion criteria are presented in Supplementary). To minimize

selection bias, investigator or sub-investigator were required to begin to invite all his/her eligible patients to participate in the study consecutively as the patients come into the clinic from the study initiation until enrolment completion and no sampling procedure were applied in this study. Three out of the 11 participating hospitals were located in tier 1 cities (Beijing and Shanghai), and eight others were located in tier 2 cities (Harbin, Changchun, Xi'an, Wuhan, Chengdu, Chongqing, Fuzhou, and Nanning).

Data collection

Data were collected at enrolment (baseline data), follow-up periods, and end of study visit (study completion/death/early termination of data entry) and recorded in an electronic case report form. Follow-up data were collected every three months in the first half year after patient enrolment and every six months thereafter.

Variable and outcome measurements

Study variables included demographic characteristics, socioeconomics, basic medical information, NSCLC diagnosis, disease characteristics, and treatment strategies. OS was defined as the time from the date of first-line treatment initiation to death from any cause. For patients who were not reported as dead at the time of analysis, their OS was administratively censored at the date when they were last known to be alive, or October 31st, 2018 (when this study ended), whichever came first.

Statistical analysis

Comparisons of patients' characteristics at baseline, disease characteristics, and first-line treatment strategies between the two tiers of cities were conducted by Chi-square tests if the sample size of a categorical variable was ≥30; If the sample size <30 or the expected value in any cell was below 5, Fisher's exact tests were used instead. A two-tailed *P*-value <0·05 was considered statistically significant. Kaplan-Meier methodology was used to estimate median OS stratified by the two city tiers. Univariate and multivariate Cox proportional regression models were developed to evaluate potential risk factors for poor survival among patients with advanced NSCLC. All variables considered to be associated with survival based on clinical judgement or prior literature[17–21] were entered into the univariate Cox regression model. Variables that yielded a *P*-value <0·05 from the univariate model were included in the multivariate model. Variables that maintained a *P*-value <0·05 in the multivariate model were considered potential risk factors for poor survival, and the hazard ratio (HR) with corresponding 95% confidence interval (CI) were reported. We used mean and mode imputation for missing value. Mean (for continuous variables) or mode (for category variables) were used to impute the missing values. All statistical analyses were conducted in SAS (Version 9·4, Cary, NC).

Role of the funding source

F Hoffmann-La Roche was the funder of the study. The study was designed by the funder and the principal investigator (Prof. Yuankai Shi). Patient recruitment was conducted by investigators and data were analysed and interpreted by the funder, with the authors and investigators.

Results

Study population

In total, 1405 patients were initially invited to the study, and 1376 patients signed the informed consent. Among them, 52 patients (including 47 patients not meeting inclusion/exclusion criteria, 4 patients without American Joint Committee on Cancer/ International Union against Cancer Staging System available, and 1 patient with missing age information) were further excluded, and a total of 1324 eligible patients were included in this study. All 1324 patients were enrolled from June 26th, 2015 to April 28th, 2017 with a median follow-up duration of 15·0 (range: 0·0–42·1) months, of which 643 died, 324 were lost-to-follow-up, and 357 were alive by the end of the study. Patients in tier 1 cities were followed around 5 months longer compared with patients in tier 2 cities (18·2 vs 13·0 months).

Patient demographic, socioeconomic and disease characteristics

The median age of enrolled 1324 advanced NSCLC patients was 60·0 (range: 21–89) years old. The majority (65·1%, 862/1324) were male, 57·4% (760/1324) lived in the urban area, and 60% (800/1324) were seen for care in hospitals locating in tier 2 cities. Overall, 60·7% (804/1324) of patients did not receive education at high school, 88·3% (1169/1324) were not covered by a private insurance, and 73·9% (979/1324) had an annual household income less than 70,000 Chinese Yuan (CNY). A total of 54·8% (725/1324) had a smoking history (defined as having smoked at least 100 cigarettes in their entire life) and 40·0% (529/1324) of patients were overweight (defined as baseline body mass index ≥23 kg/m^2). Compared with patients in tier 2 cities, patients in tier 1 cities were more likely to live in urban areas, had a higher education degree, were overweight, had a higher annual household income, and did not smoke (Table 1).

A total of 82·4% (1091/1324) of patients had Stage IV disease at diagnosis, 233 (17·6%) patients had Stage IIIB disease, and 76·6% (1014/1324) were non-squamous NSCLC. 83·5% (1106/1324) of patients had at least one

	Tier 1 (*N* = 524), *n* (%)	Tier 2 (*N* = 800), *n* (%)	Total (*N* = 1324), *n* (%)	*P*-value†
Age (years)				0·207
<65	359 (68·5%)	574 (71·8%)	933 (70·5%)	
≥65	165 (31·5%)	226 (28·3%)	391 (29·5%)	
Gender				0·121
Male	328 (62·6%)	534 (66·8%)	862 (65·1%)	
Female	196 (37·4%)	266 (33·3%)	462 (34·9%)	
Type of the longest resident place				<0·001
Rural	185 (35·3%)	369 (46·1%)	554 (41·8%)	
Urban	332 (63·4%)	428 (53·5%)	760 (57·4%)	
Unknown/not recorded	7 (1·3%)	3 (0·4%)	10 (0·8%)	
Education				<0·001
High school above	210 (40·1%)	248 (31·0%)	458 (34·6%)	
Below high school	285 (54·4%)	519 (64·9%)	804 (60·7%)	
Unknown/not record	29 (5·5%)	33 (4·1%)	62 (4·7%)	
Household annual income (after tax, CNY)				<0·001
>70000	192 (36·6%)	119 (14·9%)	311 (23·5%)	
<=70000	317 (60·5%)	662 (82·8%)	979 (73·9%)	
Unknown/not record	15 (2·9%)	19 (2·4%)	34 (2·6%)	
Private insurance				0·506
Yes	39 (7·4%)	66 (8·3%)	105 (7·9%)	
No	473 (90·3%)	696 (87·0%)	1169 (88·3%)	
Unknown	12 (2·3%)	38 (4·8%)	50 (3·8%)	
Baseline BMI (kg/m^2)				<0·001
Underweight (<18·5)	18 (3·4%)	50 (6·3%)	68 (5·1%)	
Normal (≥18·5 and <23)	181 (34·5%)	296 (37·0%)	477 (36·0%)	
Overweight (≥23)	246 (46·9%)	283 (35·4%)	529 (40·0%)	
Unknown/not record	79 (15·1%)	171 (21·4%)	250 (18·9%)	
Smoke at least 100 cigarettes in the entire life				<0·001
Yes	257 (49·0%)	468 (58·5%)	725 (54·8%)	
No	261 (49·8%)	322 (40·3%)	583 (44·0%)	
Unknown	6 (1·1%)	10 (1·3%)	16 (1·2%)	
Disease stage				0·480
IIIB	97 (18·5%)	136 (17·0%)	233 (17·6%)	
IV	427 (81·5%)	664 (83·0%)	1091 (82·4%)	
Histological type				0·734
Non-squamous	398 (76·0%)	616 (77·0%)	1014 (76·6%)	
Squamous	106 (20·2%)	172 (21·5%)	278 (21·0%)	
Undetermined	20 (3·8%)	12 (1·5%)	32 (2·4%)	
Patients with metastatic lesion				0·104
Yes	427 (81·5%)	679 (84·9%)	1106 (83·5%)	
No	97 (18·5%)	121 (15·1%)	218 (16·5%)	
Relevant gene test				0·010
Yes	365 (69·7%)	515 (64·4%)	880 (66·5%)	
No	142 (27·1%)	276 (34·5%)	418 (31·6%)	
Missing	17 (3·2%)	9 (1·1%)	26 (2·0%)	
ECOG PS at baseline				<0·001
0	256 (55·1%)	155 (26·4%)	411 (39·0%)	
1	181 (38·9%)	416 (70·7%)	597 (56·7%)	
2+	28 (6·0%)	17 (2·9%)	45 (4·3%)	
Total	465 (100%)	588 (100%)	1053 (100%)	

***Table 1*: Demographics, socioeconomics and basic medical information at baseline by level of the city.**
Abbreviation: CNY, Chinese Yuan; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PS, performance status. †P value is calculated after excluding the patients for whom the information of the corresponding variable was missing.

	Tier 1 (*N* = 524), *n* (%)	Tier 2 (*N* = 800), *n* (%)	Total (*N* = 1324), *n* (%)	*P* value†
Gene aberration characteristics				
***EGFR* tested**	230 (43·9%)	353 (44·1%)	583 (44·0%)	0·794
EGFR mutations	101 (43·9%)	179 (50·7%)	280 (48·0%)	0·108
Exon 19 deletion + Exon 21 L858R	86 (37·4%)	157 (44·5%)	243 (41·7%)	
EGFR wild type	129 (56·1%)	174 (49·3%)	303 (52·0%)	
EGFR untested	277 (52·9%)	438 (54·8%)	715 (54·0%)	
EGFR missing	17 (3·2%)	9 (1·1%)	26 (2·0%)	
***EML4-ALK* rearrangement tested**	84 (16·0%)	141 (17·6%)	225 (17·0%)	0·553
EML4-ALK rearrangement (Yes)	28 (33·3%)	18 (12·8%)	46 (20·4%)	<0·001
EML4-ALK rearrangement (No)	56 (66·7%)	123 (87·2%)	179 (79·6%)	
EML4-ALK rearrangement untested	423 (80·7%)	649 (81·1%)	1072 (81·0%)	
EML4-ALK rearrangement missing	17 (3·2%)	10 (1·3%)	27 (2·0%)	
***ROS1* rearrangement tested**	46 (8·8%)	64 (8·0%)	110 (8·3%)	0·535
ROS1 rearrangement (Yes)	2 (4·3%)	12 (18·8%)	14 (12·7%)	0·025
ROS1 rearrangement (No)	44 (95·7%)	52 (81·3%)	96 (87·3%)	
ROS1 rearrangement untested	461 (88·0%)	727 (90·9%)	1188 (89·7%)	
ROS1 rearrangement missing	17 (3·2%)	9 (1·1%)	26 (2·0%)	

***Table 2*: Gene aberration characteristics at baseline by level of the city.**
Abbreviation: EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; *ROS1, ROS* proto-oncogene, receptor tyrosine kinase 1. †P value is calculated after excluding the patients for whom the information of the corresponding variable was missing.

metastatic lesion. Among 79·5% (1053/1324) of patients with their baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) evaluated, the majority had ECOG PS of 0 or 1 (ECOG PS =0, 39·0% [411/1053]; ECOG PS=1, 56·7% [597/1053]). Patients receiving treatment in tier 1 cities tended to have a higher gene test rate (tier 1 vs tier 2: 69·7% vs 64·4%, P = 0·010) and better functional status at baseline (ECOG PS=0, tier 1 vs tier 2: 55·1% vs 26·4%, P < 0·001) (Table 1).

Gene tests

In total, 66·5% (880/1324) of patients received at least one relevant gene test. Test rates were 44·0% (583/1324) for *EGFR* mutations, 17·0% (225/1324) for *EML4-ALK* gene fusions, and 8·3% (110/1324) for *ROS1* gene fusions. Gene aberration rates were 48·0% (280/583) for *EGFR*, 20·4% (46/225) for *EML4-ALK*, and 12·7% (14/110) for *ROS1*. Furthermore, of *EGFR* mutated patients, there were 86·8% (243/280) with deletions in exon 19 and point mutations in exon 21. A similar proportion of patients received *EGFR* gene test in tier 1 cities comparing to tier 2 cities (43·9% [230/524] vs 44·1% [353/800], P = 0·794), and the *EGFR* mutation positive rates were also similar between tier 1 and tier 2 cities (43·9% [101/230] vs 50·7% [179/353], P = 0·108). There was no obvious difference in *EML4-ALK* and *ROS1* testing rates between two tier cities, but patients in tier 1 cities were more likely to have a positive *EML4-ALK* result compared with those in tier 2 cities (33·3% [28/84] vs 12·8% [18/141], P < 0·001). However, patients in tier 1 cities had a higher negative rate of *ROS1* gene fusions than those in tier 2 cities (95·7% [44/46] vs 81·3% [52/64], P = 0·025) (Table 2).

Treatment strategies at first line: an overall description

In first-line setting, 83·5% (1105/1324) of patients received chemotherapy (Table 3). Among platinum-based regimens, cisplatin was the most predominated platinum agent (57·6%, 637/1105), followed by carboplatin (20·1%, 222/1105) and nedaplatin (17·9%, 198/1105). For non-platinum chemotherapy-backbone agents, pemetrexed was prescribed most frequently (51·9%, 574/1105), followed by docetaxel (16·5%, 182/1105) and paclitaxel (15·2%, 168/1105). There were 30·9% (409/1324) of patients receiving targeted therapy in the first-line setting. Of patients receiving targeted therapies, 33·3% (136/409) received gefitinib, and the corresponding proportion was 21·0% (86/409), 9·8% (40/409), 0·5% (2/409), and 0·5% (2/409), for icotinib, erlotinib, afatinib, and osimertinib, respectively, as EGFR-Tyrosine kinase inhibitors (TKIs). Only one ALK-TKI (crizotinib) was observed, and 5·1% (21/409) of patients received crizotinib as first-line treatment. Besides TKIs, 22·2% (91/409) of patients received recombinant human endostatin and 10·3% (42/409) of patients received bevacizumab as first-line treatment. Among 233 patients with Stage IIIB disease, 223 patients received chemotherapy including 55 patients treated with definitive concurrent chemoradiotherapy, 46 patients received targeted therapy, and 3 patients received surgery in the first-line setting.

	Tier 1 (*N* = 524), *n* (%)	Tier 2 (*N* = 800), *n* (%)	Total (*N* = 1324), *n* (%)	*P* value
Chemotherapy				
Patients with first-line chemotherapy	449 (85·7%)	656 (82·0%)	1105 (83·5%)	0·077
Platinum compounds				
Cisplatin	335 (74·6%)	302 (46·0%)	637 (57·6%)	<0·001
Carboplatin	101 (22·5%)	121 (18·4%)	222 (20·1%)	0·099
Nedaplatin	8 (1·8%)	190 (29·0%)	198 (17·9%)	<0·001
Paraplatin	1 (0·2%)	29 (4·4%)	30 (2·7%)	<0·001
Lobaplatin	0	18 (2·7%)	18 (1·6%)	<0·001
Oxaliplatin	2 (0·4%)	2 (0·3%)	4 (0·4%)	>0·999
Folic acid analogues				
Pemetrexed	300 (66·8%)	274 (41·8%)	574 (51·9%)	<0·001
Taxanes				
Docetaxel	12 (2·7%)	170 (25·9%)	182 (16·5%)	<0·001
Paclitaxel	67 (14·9%)	101 (15·4%)	168 (15·2%)	0·829
Paclitaxel liposome	4 (0·9%)	1 (0·2%)	5 (0·5%)	0·165
Pyrimidine analogues				
Gemcitabine	84 (18·7%)	101 (15·4%)	185 (16·7%)	0·148
Fluorouracil	2 (0·4%)	0	2 (0·2%)	0·165
Tegafur	0	1 (0·2%)	1 (<0·1%)	>0·999
Vinca alkaloids and analogues				
Vinorelbine	2 (0·4%)	22 (3·4%)	24 (2·2%)	0·001
Podophyllotoxin derivatives				
Etoposide	2 (0·4%)	4 (0·6%)	6 (0·5%)	>0·999
Other antineoplastic agents	0	4 (0·6%)	4 (<0·6%)	0·151
Targeted Therapy				
Patients with first-line targeted therapy	149 (28·4%)	260 (32·5%)	409 (30·9%)	0·117
TKIs				
Gefitinib (EGFR-TKI)	38 (25·0%)	98 (37·7%)	136 (33·3%)	0·012
Icotinib (EGFR-TKI)	31 (20·9%)	55 (21·2%)	86 (21·0%)	0·934
Erlotinib (EGFR-TKI)	27 (16·9%)	13 (5·0%)	40 (9·8%)	<0·001
Osimertinib (EGFR-TKI)	0	2 (0·8%)	2 (0·5%)	0·536
Afatinib (EGFR-TKI)	2 (1·3%)	0	2 (0·5%)	0·132
Crizotinib (ALK-TKI)	10 (6·8%)	11 (4·2%)	21 (5·1%)	0·274
Apatinib (VEGFR -TKI)	2 (1.3%)	3 (1.2%)	5 (1.2%)	>0.999
Brigatinib (ALK-TKI)	1 (0.7%)	0	1 (0.2%)	0.364
Anti-angiogenic agent				
Recombinant human endostatin	25 (16·8%)	66 (25·4%)	91 (22·2%)	0·044
VEGF/VEGFR monoclonal antibody				
Bevacizumab	22 (14·8%)	20 (7·7%)	42 (10·3%)	0·023

***Table 3*: First-line treatment strategies by level of the city.**
Abbreviation: TKIs, tyrosine kinase inhibitors; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Treatment strategies at first line by city tier

In first-line settings, a similar proportion of patients from tier 1 and tier 2 cities received chemotherapy (tier 1: 85·7%, 449/524; tier 2: 82·0%, 656/800, $P = 0·077$). Compared with that of tier 2 cities, a higher proportion of patients in tier 1 cities received cisplatin (74·6% vs 46·0%, $P < 0·001$) and pemetrexed (66·8% vs 41·8%, $P < 0·001$). Patients in tier 2 cities were more likely to take nedaplatin (29·0% vs 1·8%, $P < 0·001$) and docetaxel (25·9% vs 2·7%, $P < 0·001$) than patients in tier 1 cities (Table 3).

Overall, 28·4% (149/524) of patients in tier 1 cities and 32·5% (260/800) of patients in tier 2 cities received targeted therapy as the first-line treatment. A similar proportion of patients in both tiers received EGFR-TKIs (65·8% [98/149] vs. 64·6% [168/260]), and gefitinib was the most frequently used EGFR-TKI in tier 1 cities and tier 2 cities. A greater proportion of patients in tier 1 cities (16·9%, 27/149) received erlotinib than patients in tier 2 cities (5·0%, 13/260) ($P < 0·001$); whereas a higher proportion of patients in tier 2 cities (37·7%, 98/260) received gefitinib than that of patients in tier 1

	EGFR tested (*N* = 583), *n* (%)	*EGFR* mutations (*N* = 280), *n* (%)	*EGFR* wild type (*N* = 303), *n* (%)	*EGFR* untested (*N* = 715), *n* (%)	*P* value	
					EGFR tested vs. untested	*EGFR* mutations vs. wild type
Detailed type of treatments						
Chemotherapy	405 (69·5%)	130 (46·4%)	275 (90·8%)	676 (94·5%)	<0.001	<0.001
Targeted therapy	268 (46·0%)	191 (68·2%)	77 (25·4%)	136 (19·0%)	<0.001	<0.001
TKIs						
Gefitinib (EGFR-TKI)	110 (41.0%)	97 (50.8%)	13 (16.9%)	26 (19.1%)	<0.001	<0.001
Icotinib (EGFR-TKI)	61 (22.8%)	55 (28.8%)	6 (7.8%)	23 (16.9%)	0.171	<0.001
Erlotinib (EGFR-TKI)	30 (11.2%)	25 (13.1%)	5 (6.5%)	10 (7.4%)	0.222	0.121
Osimertinib (EGFR-TKI)	2 (0.7%)	2 (1.0%)	0	0	0.552	NA
Afatinib (EGFR-TKI)	1 (0.4%)	0	1 (1.3%)	1 (0.7%)	NA	0.287
Crizotinib (ALK-TKI)	17 (6.3%)	2 (1.0%)	15 (19.5%)	4 (2.9%)	0.145	<0.001
Brigatinib (ALK-TKI)	1 (0.4%)	0	1 (1.3%)	0	NA	0.287
Apatinib (VEGFR-TKI)	0	0	0	5 (3.7%)	0.004	NA
Anti-angiogenic agent						
Recombinant human endostatin	33 (12.3%)	11 (5.8%)	22 (28.6%)	56 (41.2%)	<0.001	<0.001
VEGF/VEGFR monoclonal antibody						
Bevacizumab	25 (9.3%)	8 (4.2%)	17 (22.1%)	16 (11.8%)	0.443	<0.001

***Table 4*: First-line treatment strategies by *EGFR* status.**
Abbreviation: TKIs, tyrosine kinase inhibitors; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; VEGF, vascular endothelial growth factor;VEGFR, vascular endothelial growth factor receptor.

cities (25·0%, 38/149) (P = 0.012). Besides TKIs, the proportion of patients receiving recombinant human endostatin was relatively lower in tier 1 cities compared with tier 2 cities (16·8% [25/149] vs. 25·4% [66/260], P = 0·044), and the proportion of patients receiving bevacizumab was almost doubled in tier 1 cities compared with tier 2 cities (14·8% [22/149] vs. 7·7% [20/260], P = 0·023) (Table 3).

First-line treatment strategies by *EGFR* status

Among patients with *EGFR* tested, 69·5% (405/583) received chemotherapy and 46·0% (268/583) received targeted therapy in the first-line setting. Of those with *EGFR* wild type, the proportions of patients received chemotherapy and targeted therapy were 90·8% (275/303) and 25·4% (77/303), respectively. Among these patients treated with targeted therapy, 53·2% (41/77), 28·6% (22/77), and 22·1% (17/77) received TKIs, recombinant human endostatin, and bevacizumab, respectively. Of those with *EGFR* mutation, 46·4% (130/280), 68·2% (191/280), and 63·9% (179/280) received chemotherapy, targeted therapy, and EGFR-TKIs, respectively. For those patients who did not receive *EGFR* test, 94·5% (676/715) received chemotherapy and 19·0% (136/715) received targeted therapy (Table 4). Among these patients who received targeted therapy, 50·7% (69/136), 41·2% (56/136), and 11·8% (16/136) received TKIs, recombinant human endostatin, and bevacizumab, respectively.

Among patients with *EGFR* mutation, 63·9% (179/280) received EGFR-TKIs in first-line setting, and gefitinib was the most frequently used EGFR-TKI (34·6%, 97/280), followed by icotinib (19·6%, 55/280) and erlotinib (8·9%, 25/280). In addition, 8·4% (60/715) of *EGFR* untested patients received EGFR-TKIs as first-line treatment (Table 5).

OS and associated risk factors

A total of 48·6% (643/1324) deaths were recorded. The median OS was 23·2 (95%CI 19·5–25·5) months for all eligible patients. OS rates at 3, 6, 9, 12, and 36 months were 94·9%, 85·3%, 77·4%, 68·9%, and 39·0%, respectively. Substantial difference of median OS was observed between the two tiers (tier 1: 35·4 [95%CI 25.9-not available] months vs tier 2: 16·3 [95%CI 14.6–19.6] months, P < 0·001) (Figure 1). Median OS was more than one year longer in patients with *EGFR* mutation

	EGFR mutations (*N* = 280), *n* (%)	*EGFR* untested (*N* = 715), *n* (%)
EGFR-TKI treatment	**179 (63·9%)**	**60 (8·4%)**
Gefitinib	97 (34·6%)	26 (3·6%)
Icotinib	55 (19·6%)	23 (3·2%)
Erlotinib	25 (8·9%)	10 (1·4%)
Afatinib	0	1 (0·1%)
Osimertinib	2 (0·7%)	0

***Table 5*: First-line EGFR-TKI treatment strategies by *EGFR* status.**
Abbreviation: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitors.

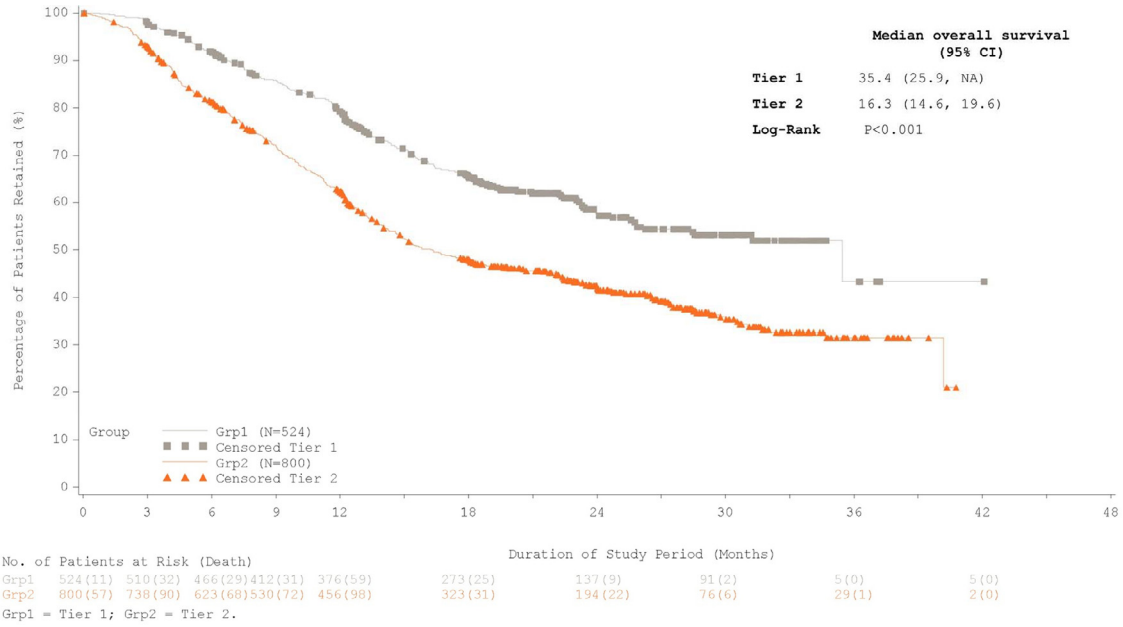

Figure 1. Kaplan-Meier curve of overall survival by tier level.

compared with patients with *EGFR* wild type (34·7 [95%CI 27.4-not available] months vs. 18·1 [95%CI 15.2 −23.2] months, $P < 0·001$) (Figure 2).

Multivariate analyses showed males (hazard ratio [HR] 1·32, 95% CI 1·03–1·69), education level below high school (HR 1·29, 95%CI 1·09–1·53), receiving treatment in tier 2 cities (HR 1·69, 95%CI 1·42–1·99), smoking history (HR 1·42, 95%CI 1·13–1·79), and more than one metastasis lesion (HR 1·61, 95%CI, 1·38–1·88) were significant risk factors for death (Table 6).

Discussion

To the best of our knowledge, this is the first prospective, multicentre study to investigate the treatment strategies and OS among patients with unresectable Stage

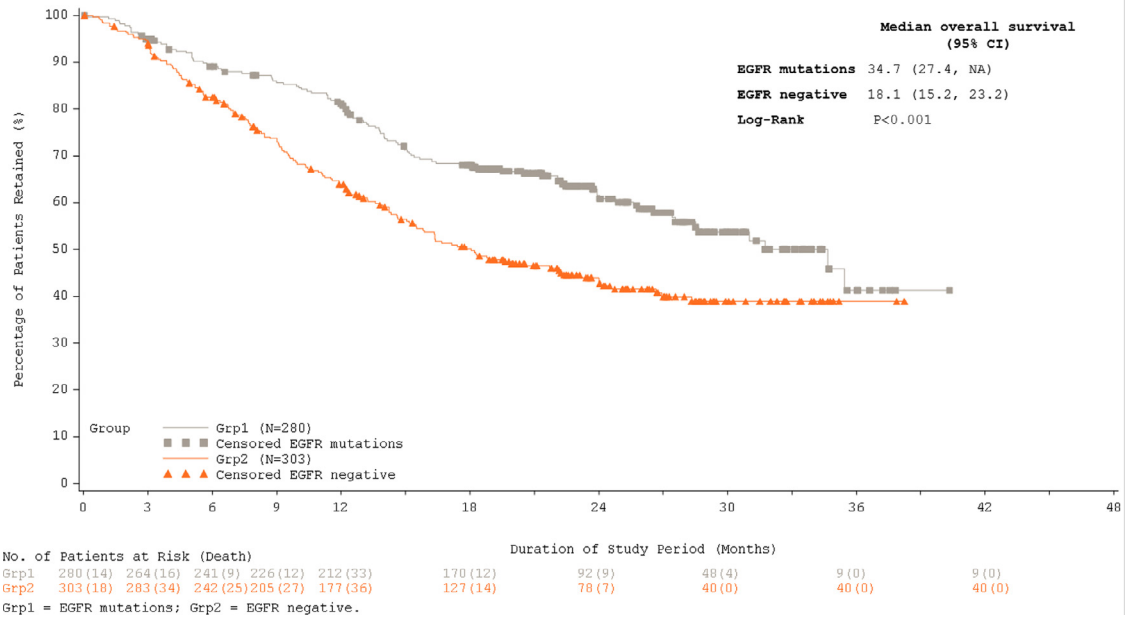

Figure 2. Kaplan-Meier curve of overall survival by *EGFR* mutations status.

Variables	HR	95% CI	*P* value
Univariate analysis (*N* = 1324)			
Age (>=65 vs· <65)	1·16	(0·98, 1·37)	0·081
Sex (Male vs· Female)	1·65	(1·39, 1·96)	<0·001
BMI (underweight vs· Normal)	1·35	(0·97, 1·87)	0·069
BMI (overweight vs· Normal)	0·91	(0·78, 1·08)	
Education (Below high school vs· High school above)	1·33	(1·12, 1·57)	0·001
Household annual income (<=70000 CNY vs· >70000 CNY)	1·43	(1·17, 1·74)	<0·001
Private insurance (No vs· Yes)	1·32	(0·97, 1·79)	0·076
Tier (Tier 2 vs· Tier 1)	1·74	(1·47, 2·05)	<0·001
Smoking history (Yes vs· No)	1·70	(1·45, 1·99)	<0·001
Disease stage (IV vs· IIIB)	1·20	(0·97, 1·48)	0·099
Histology type (Non-squamous vs· Squamous)	0·77	(0·65, 0·92)	0·005
More than one metastasis lesion (Yes vs· No)	1·46	(1·25, 1·71)	<0·001
Gene test (No vs· Yes)	1·15	(0·98, 1·36)	0·092
ECOG PS (1 vs· 0)	1·20	(1·03, 1·41)	0·065
ECOG PS (2+ vs· 0)	1·18	(0·78, 1·79)	
Multivariate analysis			
Sex (Male vs· Female)	1·32	(1·03, 1·69)	0·025
Education (Below high school vs· High school above)	1·29	(1·09, 1·53)	0·003
Tier (Tier 2 vs· Tier 1)	1·69	(1·42, 1·99)	<0·001
Smoking History (Yes vs· No)	1·42	(1·13, 1·79)	0·002
More than one metastasis lesion (Yes vs· No)	1·61	(1·38, 1·88)	<0·001

***Table 6*: Univariate and multivariate Cox regression analysis for potential risk factors.**
Abbreviation: CNY, Chinese Yuan; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PS, performance statues.

IIIB or IV NSCLC stratified by the tier of cities in China. In addition, this study provided a comprehensive description of patient profiles, and examined which potential risk factors were associated with poor survival.

In this study, patients' demographics, socio-economics, and the phenomenon that most patients were in stage IV when first diagnosed were similar to those reported in a previous study in China.[22] Moreover, we found that the majority of patients in our study had ECOG PS 0-1, which was also consistent with previous studies.[10,23]

According to our results, 44%, 17%, and 8·3% patients received *EGFR, EML4-ALK,* and *ROS1* gene test, respectively. These testing coverage rates were relatively lower than results reported from previous cross-sectional studies in China.[24] The difference in test rate is mainly due to difference on the histological type of included patients. Overall, 21·5% of patients in our study had squamous cell carcinoma with significantly lower mutation rate, compared with less than 5% of patients had squamous cell carcinoma in the previous study.[24] The Chinese guideline on diagnosis and treatment of primary lung cancer (2015 version) has recommended that for advanced NSCLC patients, *EGFR, ALK,* and *ROS1* detection should be routinely performed at the time of diagnosis.[25] Given our findings of low testing coverage rate, the scale-up of gene test among advanced NSCLC patients was needed. Among patients receiving corresponding gene tests, positive rate was 48·0% for *EGFR* mutation, with that of 20·4% and 12·7% for *EML4-ALK* rearrangement and *ROS1* rearrangement, respectively. The rearrangement rates for *EML4-ALK* and *ROS1* were higher than expected as well as the results from previous studies in China.[26,27] The possible reason might mainly be the low testing rate for these two gene alterations as well as a highly selective population for testing in our study. As per the real clinical practice in China during the enrolment period of this study, the testing for *EML4-ALK* and *ROS1* rearrangement were not so widely adopted as that for *EGFR* mutation. The only available ROS1-TKI at that time, crizotinib, had not been approved by US Food and Drug Administration for patients with *ROS1* rearrangement until March 11st, 2016. Many patients would receive *EML4-ALK* or *ROS1* testing only after the *EGFR* mutation status was confirmed negative, which would contribute to a high enriched population for *EML4-ALK* or *ROS1* rearrangement. In addition, the small sample size of tested population may also lead to the variability of testing results. Therefore, the results should be interpreted with cautions.

In our study, most NSCLC patients received chemotherapy in first-line setting and platinum compounds were most often used chemotherapy; this was in line with the standard first-line treatment for advanced NSCLC recommended in China in 2015, the US, and

other countries.[25,28,29] Our study also found that about 30% of patients received targeted therapy including TKIs, recombinant human endostatin, and Bevacizumab, regardless of gene alterations. This is similar to the result reported in one previous study.[24] In that study, 67% of patients who were *EGFR* mutation positive received EGFR-TKIs as first-line treatment, and our study also only found 63·9% of *EGFR* mutated patients received EGFR-TKI therapy in the first-line setting. Moreover, our findings also revealed that 8·4% of *EGFR*-untested patients still received EGFR-TKIs as first-line treatment although recent guidelines recommended patients with advanced non-squamous NSCLC should be tested for *EGFR* mutation before initiation of first-line treatment.[25,30–32] This discrepancy may reflect that in real-world settings, many factors such as physician experience and patients' attitudes could influence the decision of treatment.

Our findings showed that the median OS for all eligible NSCLC patients was 23·2 months, and the 1-year OS rate was 68·9%. This finding was better than the survival reported from a large population-based cohort study in China conducted in 2011-2013[33] where 1-year OS rate was 58·9% among patients with Stage IIIb/IV NSCLC. The improved survival in our study may reveal a longer survival trend for Chinese patients with advanced NSCLC. Our study also found that the median OS was significantly longer in patients with *EGFR* mutation compared with patients with *EGFR* wild type (34·7 months vs. 18·1 months, $P < 0·001$), which indicated that EGFR-TKIs brought much benefit for Chinese NSCLC patients with *EGFR* mutation.

The remarkable gap on OS between NSCLC patients in tier 1 cities and tier 2 cities were found in our study. The reason resulting in our findings that tier 1 patient had better OS than their tier 2 counterparts remained unclear. Since this study only analysed crude OS and there was significant difference in baseline characteristics between two tier levels that have not been adjusted for, further research investigating survival stratified by tiers of cities in a more sophisticated way was warranted.

Our study also suggested that male, education below high school, tier 2 cities, smoking history, and multiple metastases were associated with suboptimal survival outcome, which was consistent with findings from other studies. Pinto et al.[34] and Salloum et al.[35] found that compared to female, male NSCLC patients had a higher risk of death. According to U.S. Department of Health and Human Services, smoking contributed at least 80% of mortality among patients with lung cancer.[36] Lee et al.[37] also showed that survival time was significantly longer among never-smoke NSCLC patients. In terms of education level and city tier, a nationwide population-based study[38] conducted in Sweden revealed that in patients with early stage lung cancer, low education level was associated with poor survival. Also, Vanthomme et al.[39] found that socio-economic position including education and housing conditions was associated with mortality in lung cancer. These findings could help explain why we found that lower education level and tier 2 cities were associated with mortality. Lastly, several studies[40–43] had already showed that metastasis was associated with poor survival.

There are some limitations in this study. First, same as other observational studies using medical records, the observed OS may be biased by loss to follow up. Second, although patients were selected from a pooled socially and geographically representative sites across China, disparities regarding health care and economic status may exist between hospital sites, resulting in selection bias. Besides, some of the enrolled patients with stage IIIB underwent radiotherapy concurrently with chemotherapy as a standard practice, but we did not collect detailed data on radiotherapy (dose, fractionation, etc.). Therefore, we could not perform analyses to explore the potential significance of these factors for predicting survival in the subgroup of Stage IIIB patients. In China, the third generation EGFR-TKI osimertinib was approved on Mar 22th, 2017,[44] the first 2nd generation ALK-TKI ceritinib was approved on May 31st 2018,[45] and the first programmed death 1 monoclonal antibody nivolumab was approved on Jun 15th, 2018.[46] As this study enrolled patients from June 26th, 2015 to April 28th, 2017 with follow up till October 31st, 2018, it reveals the real-world situation of clinical profile, treatment strategies and prognosis for unresectable Stage IIIB or IV NSCLC patients before these kinds of drugs approved in China.

Conclusion

In summary, this is the first prospective study investigating the clinical profile, treatment strategy, OS, and risk factors of mortality among patients with unresectable Stage IIIB or IV NSCLC in China and examining the difference between city tiers. Our results demonstrated a survival benefit in *EGFR* mutant patients and those in tier 1 cities. Our study also provided a comprehensive view of evidence-based treatment choices in China before the era of the third generation EGFR-TKI, the second generation ALK-TKI and immunotherapy. Some potential risk factors of death among these patients were also identified and further studies are warranted.

Contributors

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Angela Yin - validation, writing – original draft, and writing – review & editing
Yigong Zhou - validation, writing – original draft, and writing – review & editing

Data sharing

De-identified individual participant data, data dictionary, protocol, and consent forms can be requested via the corresponding author and will be available once all results from the study have been published assuming appropriate ethics approval is achieved.

Declaration of interests

All authors have completed the ICMJE uniform disclosure form.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100452.

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