Study of the relationship between *EGFR* mutation status and bone metastasis in advanced lung adenocarcinoma.

Xiaoye Ai, Adalati Yasheng, Zhennan Zhangjia, Ying Tong, Bing Zhao[*]

Tumor Hospital Affiliated to Xinjiang Medical University, Urumqi, PR China

Abstract

To investigate the relationship between *EGFR* gene status and bone metastasis in lung adenocarcinoma, we collected the data of 331 patients with advanced lung cancer, and the status of *EGFR* mutation was detected by RT-PCR. Follow-ups of these patients were performed. In these patients, the *EGFR* mutation rate was 52.2%. The incidence of bone metastases (54.9%) and brain metastases (29.4%) with *EGFR* mutant patients was higher than that of the wild-type EGFR patients. Compared with the number of metastases, *EGFR* mutant bone metastases were more than 2 and more, and the proportion of wild type single-site metastasis was more. The median survival of bone metastases in advanced lung adenocarcinoma was 14.7 months. Mutant EGFR group, bone metastasis group median survival in 18.2 months, no bone metastasis group median survival in 21.8 months. In the wild-type group, the median survival of the bone metastases group was 11.5 months, and the median survival in the non-bone metastases group was 15.5 months. *EGFR* mutations are more likely to develop bone metastasis and brain metastasis in patients with advanced lung adenocarcinoma.

Introduction

In China, lung cancer has become the malignant tumor with the highest morbidity and mortality. Most patients are diagnosed with advanced lung cancer at the first-time consultancy and lose the chance to be cured by surgery. According to relevant statistics, the incidence of bone metastasis ranges from 41%-58% in patients with lung cancer [1,2].

The time interval between incidence of bone metastasis and occurrence of Skeletal-Related Event (SRE) is 9.5 months [2]. In lung adenocarcinoma of the Asian patients, gene mutations of the epidermal growth factor receptor occur in about 40%-60% [3-5]. It is reported in some researches that, the incidence rate of bone metastasis before occurrence of the Tyrosine Kinase Inhibitor (TKI) is 20% and increases to 27% after occurrence of TKI [2]. It means that the incidence rate of bone metastasis changes substantially along with the occurrence and utilization of TKI.

This study provides a retrospective analysis of correlation between *EGFR* mutation status and bone metastasis through collection of medical records and follow-ups of the patients treated in our hospital from 2013-2016 (Table 1).

Methods

Object of study and methods

The patients who confirmed with stage IV lung adenocarcinoma by pathology or cytology in the Xinjiang Tumor Hospital from 2013-2016 were selected as the objects of this study.

Relevant exclusion standards are: 1. Patients with incomplete general data; 2. The *EGFR* mutation status was unknown; 3. Patients with second primary tumor; 4. Patients without complete imaging data (including chest, abdomen, and pelvic cavity, skull and bone metastasis). The complete medical records of the above mentioned patients were collected, to whom the follow-up visits were performed through phone calls or medical records.

Diagnostic criteria

EGFR gene detection: Real-time quantitative fluorescent PCR technique is adopted for detection of gene status in tissues or blood of the patients.

Diagnosis of bone metastasis: With reference to the Expert Consensus on the Diagnosis and Treatment of Bone Metastasis in Lung Cancer (2014 version).

Statistical method

SSPS17.0 software is used for statistical analysis. Measurement data is represented by (x ± s), comparison among groups is provided with t-test, enumeration data is provided with χ^2 test, survival analysis is provided with log-rank test, and statistical significance is recorded as P<0.05.

Result

Comparison of general data of the mutant EGFR group and the wild-type EGFR group

331 cases of patients from 2013-2016 are collected, 173 cases of patients with *EGFR* mutation and 158 cases of patients with wild-type, the *EGFR* mutation rate was 52.2%. The comparison of the two groups of patients is as shown in Table 2. In the mutant EGFR group, male patients account for 47.4%, and female patients account for 52.6% at the average age of 59.9 y old. Patients who smoke account for 29.5% and those who don't smoke account for 70.5%. In first-time diagnosis, patients with intrapulmonary metastases account for 49.1%, patients with brain metastases account for 29.4%, patients with

bone metastases account for 54.9% patients with liver metastases account for 19.7%, patients with pleural metastasis account for 43.4%, patients with adrenal metastasis account for 9.8%, and patients with metastases in other sites account for 9.2%. Patients with mutations in 19 exon deletions account for 52.6%, patients with mutations in 21 exon deletions account for 39.3% and patients with other type of mutations account for 8.1%. In the wild-type EGFR group, male patients account for 63.9%, and female patients account for 36.1% at the average age of 59.9 y old. Patients who smoke account for 52.2% and those who don't smoke account for 47.5%. In first-time diagnosis, patients with intrapulmonary metastases account for 43.7%, patients with brain metastases account for 20.9%, patients with bone metastases account for 38.0% patients with liver metastases account for 13.3%, patients with pleural metastases account for 34.8%, patients with adrenal metastases account for 18.48%, and patients with metastases in other sites account for 11.4%. The incidence rate of brain metastases and bone metastases in the mutant EGFR group is higher than that of the wild-type EGFR group. The incidence rate of adrenal metastases is higher than that of the mutant EGFR group (P<0.05 with statistical significance).

Table 1. The correlation between EGFR mutation status and incidence of bone metastasis.

		Mutant EGFR group	Wild-type EGFR group	P value
Bone Metastases (%)		95 (54.91%)	60 (37.97%)	0.002
Number of Metastases	1	16	21	0.015
	2	36	23	
	3 or above	43	16	
Alkaline phosphatase (mmol/L)		136.8	113	0.011

Table 2. Comparison of general data, metastasis site and EGFR gene status of the two groups of patients.

	EGFR mutant group	Wild-type EGFR group	Total	P value
Sex				
Male	82 (47.4%)	101 (63.9%)	183	0.003
Female	91 (52.6%)	57 (36.1%)	148	
Average age	59.9 ± 11.8	59.6 ± 11.3	-	0.76
	(24-68)	(28-84)		
Smoking history				
With	51 (29.5%)	83 (52.5%)	134	0
Without	122 (70.5%)	75 (47.5%)	197	
Metastasis site				
Inside the lungs	85 (49.1%)	69 (43.7%)	154	0.32
Brain	51 (29.4%)	33 (20.9%)	78	0.043
Bone	95 (54.9%)	60 (38.0%)	155 (46.8%)	0.002
Liver	34 (19.7%)	21 (13.3%)	55	0.12

Pleura	75 (43.4%)	55 (34.8%)	130	0.112
Adrenal gland	17 (9.8%)	29 (18.4%)	46	0.025
Other	16 (9.2%)	18 (11.4%)	34	
EGFR mutation				
19	91 (52.6%)	-	91	
21	68 (39.3%)	-	68	
Others	14 (8.1%)	-	10	
Wild-type	-	158	158	
Total	173 (100%)	158 (100%)	331	

Table 3. *Survival situation of the patients with bone metastasis in the mutant EGFR group and wild-type EGFR group.*

OS	With bone metastasis (month)	Without bone metastasis (month)	P value
Mutant EGFR group	18.2	21.8	0.029
Wild-type EGFR group	11.9	15.5	0.04

The relationship between EGFR mutation and incidence rate and number of bone metastases

The incidence rates of bone metastasis are 54.91% and 37.97% of the mutant EGFR group and wild-type EGFR group respectively (P<0.05 with statistical significance). In terms of the number of metastases, patients with two or above bone metastases in the mutant EGFR group take a larger proportion and most of the patients in the wild-type EGFR group are with single-site metastasis. The difference between the two groups is of statistical significance (P<0.05). Meanwhile, with regard to biochemical indicators, alkaline phosphatase in the mutant EGFR group and the wild-type EGFR group reaches 136.8 mmol/L and 113.0 mmol/L respectively, which indicates the difference is of statistical significance (P<0.05).
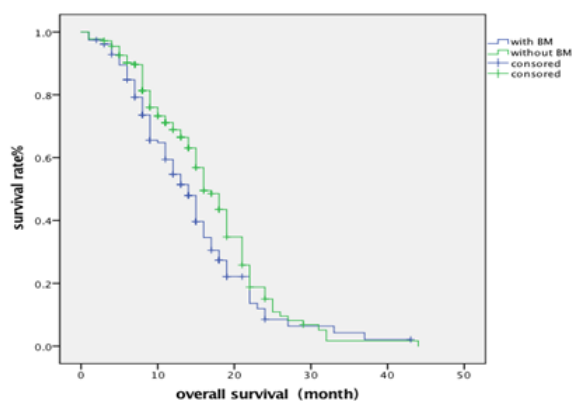

Figure 1. *Survival of the patients with bone metastasis from advanced lung adenocarcinoma.*
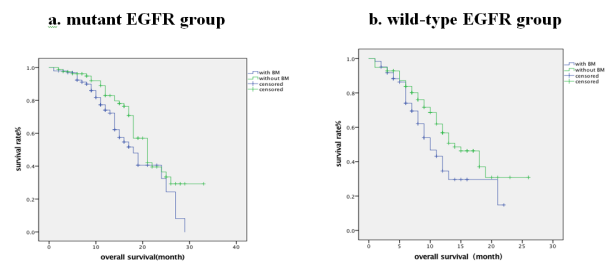

Figure 2. *Survival of the patients with bone metastasis under different EGFR mutation status.*

Survival situation of the patients with bone metastasis from advanced lung adenocarcinoma

Follow-up visits were paid to the 331 patients, of whom the survival analysis is given in Figure 1. The median overall survival of the patients is 14.7 months and 16.8 months respectively of those with and without bone metastasis. P=0.022<0.05, which means the difference is of statistical significance.

Survival situation of the patients with bone metastasis from mutant EGFR and wild-type EGFR advanced lung adenocarcinoma

Follow-up visits were paid to the patients in two group, the mutant EGFR group and wild-type group, of which, the survival analysis is as shown in Figure 2 and Table 3. In the mutant EGFR group, the median overall survival is 18.2 months and 21.8 months respectively of those with and without bone metastasis. P=0.029<0.05, which means the difference is of statistical significance. In the wild-type EGFR group, the median overall survival is 11.9 months and 15.5 months respectively of those with and without bone metastasis.

P=0.04<0.05, which means the difference is of statistical significance.

Discussion

According to the latest statistics, China is expected to have 4.292 million new cases of patients with tumor including 2.814 million cases of patients who are dead. Among all the patients, lung carcinoma is with the highest incidence rate and mortality rate [6]. Most of the patients are already in terminal stage at confirmed diagnosis, and of whom, the five-year survival rate is less than 15% [7]. With the constant advancement in genetics and genomics, it have been gradually found and proved that the key factor leading to lung cancer is gene mutation. Among those with lung adenocarcinoma, driver genes are detected in 60% to 70% of the patients [8]. These driver genes include *EGFR*, *KRAS*, *HER2*, *PIK3CA*, *BRAF*, *MET* mutations and *ALK*, *ROS1* and *RET* gene rearrangement. EGFR is a kind of cell-surface membrane protein receptor and a member of the epidermal growth factor ErbB family. When EGFR is connected with corresponding signal molecule, dimers would form among the receptor molecules, and at the same time, mutual phosphorylation of intracellular tyrosine kinases is started and intracellular cascade signalling pathways are activated, thus, a series of intracellular morphological changes are caused [9]. It is shown by relevant studies that, excessive expression of *EGFR* genes is closely related to proliferation, invasion and metastasis of lung cancer [10].

According to relevant statistics, *EGFR* mutation rate is as high as 40%-60% of Asian patients with lung cancer. EGFR-TKI treatment helps prolong the overall survival of advanced lung cancer to 21.6-21.6 months [11,12]. In the study in this paper, 331 cases of patients were collected, among whom, the *EGFR* mutation rate was 52.2%, which means the data are basically identical with the that obtained by Liu et al. [13,14]. Among all the objects of the study, female patients and non-smoking patients are the advantaged group, which is similar to the previous research results. It is also found the patients in the mutant EGFR group are more likely to develop bone metastases (54.9%) and brain metastases (29.4%).

The incidence rate of bone metastasis has changed since the clinic application of EGFR-TKI treatment. In the study in this paper, the incidence rate of bone metastasis is 46.8% and 54.9% in the mutant EGFR group, which is higher than that of the wild-type EGFR group. In addition, most of the patients in the mutant EGFR group are with multi-sites metastases and a larger proportion of the patients in the wild-type EGFR group are with single-site metastasis. However, the reason is still unknown at present, maybe EGFR signals play an important role in the process of tumor metastasis. In terms of lung cancer, EGFR signals are closely related to MET, which plays an very important role in angiogenesis and regulation of cell proliferation and haematogenous metastasis [15,16].

The median overall survival of the patients with bone metastasis is 14.7 months, which is shorter than that of the patients without bone metastasis. Thus, it can be seen that, bone metastasis often leads to poorer life quality and shorter period of survival of patients. The skeletal-related events caused by bone metastasis and the pain brought by treatment jointly severely affect the life quality of patients. On this ground, it is especially important to actively prevent and cure bone metastasis and skeletal-related events while controlling primary disease.

In *EGFR* mutation group, the median overall survival of the patients with bone metastasis and without bone metastasis is 18.2 months and 21.8 months respectively. In the wild-type EGFR group, the median overall survival of the patients with bone metastasis and without bone metastasis is 11.9 months and 15.5 months respectively. It is regarded that such result may have something to do with utilization of the TKI drugs which prolong survival of the patients in the mutant EGFR group.

Conclusion

To sum up, patients with bone metastasis of lung cancer have a shorter period of survival and easily develop SRE, which seriously affect the life quality of them. The incidence rates of bone, brain and adrenal metastasis of the patients with mutant EGFR are relatively higher. Thus, for patients with mutant EGFR, special attention shall be paid to prevention and treatment of bone metastasis during control of primary disease.

Acknowledgement

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*Correspondence to

Bing Zhao

Tumor Hospital Affiliated to Xinjiang Medical University

Urumqi

PR China