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Hepatic Metastases is Associated with Poor Efficacy of Erlotinib as 2nd/3rd Line Therapy in Patients with Lung Adenocarcinoma

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Background: Hepatocyte growth factor (HGF)-mediated mesenchymal-to-epithelial transition factor (*MET*) gene amplification is a common mechanism for acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors (*EGFR*-TKIs). *MET* gene amplification has also been associated with hepatic metastases in patients with lung cancer. The aim of this study was to investigate whether hepatic metastases are associated with decreased efficacy of erlotinib in patients with adenocarcinoma.

Material/Methods: A cohort of 329 patients with stage IV lung adenocarcinoma, known *EGFR* mutation status, and who received treatment with erlotinib in the 2nd or 3rd line setting were enrolled into this study over a period of 4 years between January 2011 and January 2015. The cohort was stratified based on the presence or absence of hepatic metastases and the efficacy of erlotinib was defined based on disease control rate (DCR) and progression-free survival (PFS).

Results: Hepatic metastases were present in 220 of the 329 enrolled lung adenocarcinoma patients. *EGFR*-activating mutations (exon 19 deletion or an exon 21 L858R mutation) were identified in 113 (34.3%) patients. The DCR was significantly lower in the hepatic metastases group than in patients without hepatic metastases (39.5% *vs.* 51.4% P=0.045). In patients with hepatic metastases, median PFS was 2.3 months in the *EGFR* mutation-positive group versus 1.4 months in the *EGFR* mutation-negative group (95% CI 1.3–3.3 *vs.* 1.3–1.5; P=0.055). Of note, erlotinib therapy in patients with hepatic metastases was complicated by elevated alanine transaminase (ALT) levels.

Conclusions: Hepatic metastasis in patients with lung adenocarcinoma predicts poor response to erlotinib as a 2nd/3rd line therapy. Combination therapy, for example with *MET*-TKI, may be a good choice for patients with liver metastases with poor prognosis.

MeSH Keywords: Adenocarcinoma • Genes, erbB-1 • Neoplasm Metastasis

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Background

Lung cancer has high mortality worldwide [1–3]. Unfortunately, most patients with non-small cell lung cancer (NSCLC) are diagnosed at an advanced stage [2]. Platinum-based doublet chemotherapy is the standard 1st line therapy for advanced NSCLC [4,5]. Single-agent chemotherapy is used in the treatment of advanced NSCLC in 2nd line therapy, while the response rate (RR) is low and all of these agents have different toxicity profiles [6,7]. Guidelines by the IASLC, CAP, and AMP recommend epidermal growth factor receptor (*EGFR*) mutation and anaplastic lymphoma kinase (*ALK)* rearrangement genetic testing of NSCLCs with an adenocarcinoma histological type or even a component of adenocarcinoma as the standard of care. Tyrosine kinase inhibitor (TKI) therapy is indicated as the standard of care for patients with adenocarcinomas that harbor *EGFR* mutations. *EGFR*-TKIs, such as gefitinib, erlotinib, icotinib, and afatinib, have been widely used not only in 1st line therapy, but also in maintenance and 2nd/3rd line therapy in advanced NSCLC [8–11].

However, some patients with *EGFR* mutation do not respond well to *EGFR*-TKIs. Additionally, nearly all the patients initially responding to *EGFR*-TKIs inevitably develop acquired resistance. Hepatocyte growth factor (HGF)-mediated mesenchymal-to-epithelial transition factor (*MET*) amplification through activating ERBB3/PI3K/AKT signaling is an important mechanism for acquired resistance to *EGFR*-TKI, and also plays an important role in the process of hepatic metastases. The incidence of hepatic metastases in patients with lung cancer is high, with rates as high as 37–51% [12–15]. Therefore, we hypothesized that hepatic metastasis predicts poor efficacy of *EGFR*-TKI [16,17].

In this study, we compared the efficacy of erlotinib in the 2nd/3rd line setting in 329 pulmonary adenocarcinoma patients stratified by the presence or absence of hepatic metastasis.

Material and Methods

Patients

From January 2011 to January 2015, 220 lung adenocarcinoma patients with hepatic metastases were enrolled into the study, and 109 stage IV lung adenocarcinoma patients without hepatic metastases were recruited continuously from January 2011. Eligible patients had confirmed stage IV lung adenocarcinoma (Union for International Cancer Control classification version 7) with a confirmed activating mutation of *EGFR* (exon 19 deletion or an exon 21 L858R mutation). All patients received 2nd/3rd line chemotherapy treatment and had platinum-based doublet chemotherapy as 1st line therapy. They also had measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST version 1.1), an Eastern Cooperative Oncology Group performance status (PS) of 0–2, age ≥18, and adequate hematological, biochemical, and organ function. Patients with unstable systemic disease or uncontrolled brain metastases were excluded. This research was approved by the Ethics Committee of Shanghai Pulmonary Hospital, Tongji University, and informed consent was obtained from all of the patients before enrollment.

Treatment

We performed history-taking, physical examination, hematologic and biochemical testing, and chest and abdomen computed tomographic scans before erlotinib treatment. Assessments of toxic effects and quality of life were obtained. Patients received erlotinib 150 mg daily. Assessment of toxicity was done according to National Cancer Institute Common Toxicity Criteria version 4.0. Patients were evaluated every 3 weeks, and hematology and blood chemistry analyses were done. Tumor size was assessed every 6 weeks [18–20].

DNA extraction and *EGFR* mutation analysis

All *EGFR* mutational analyses were performed using the Amplification Refractory Mutation System (ARMS) in Tongji University Medical School Cancer Institute (Shanghai, China). The details were described in our previous articles [21,22].

Statistical analysis

The chi-square test was used to analyze the association between hepatic metastases and clinical data and disease control rate (DCR). For the survival analysis, patients were censored at the last date at which they were known to be alive. All time-to-event outcomes, such as progression-free survival (PFS), were estimated using the Kaplan-Meier method and compared across groups with the log-rank test or the Cox proportional hazards model. The SPSS statistical package for Windows version 13.0 was used. All P values were 2-sided, and statistical significance was defined as $p<0.05$.

Results

Patient characteristics

We enrolled 329 stage IV lung adenocarcinoma patients with known *EGFR* mutation status. Table 1 shows the clinical characteristics of all the patients. Hepatic metastases was more common in patients younger than 65 years old (p=0.028), and the PS of these patients was significantly higher (p<0.001) (Table 1).

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Table 1. Characteristics of all cases.

Items	Total	Hepatic metastases			EGFR mutation		
		No	Yes	P	Negative	Positive	P
Sex, n (%)							
Male	168 (51.1%)	53 (48.6%)	115 (51.4%)	0.559	127 (58.8%)	41 (36.3%)	**<0.001**
Female	161 (48.9%)	56 (52.3%)	105 (47.7%)		89 (41.2%)	72 (63.7%)	
Age, mean	57	60	55		56	58	
<65; n (%)	251 (76.3%)	75 (68.8%)	176 (80.0%)	**0.028**	171 (79.2%)	80 (70.8%)	0.102
≥65; n (%)	78 (23.7%)	34 (31.2%)	44 (20.0%)		45(20.8%)	33 (29.2%)	
Smoking, n (%)							
Smoker	155 (47.1%)	45 (41.3%)	110 (50.0%)	0.159	121 (56.0%)	34 (30.1%)	**<0.001**
Non-smoker	174 (52.9%)	64 (58.7%)	110 (50.0%)		95 (44.0%)	79 (69.9%)	
Performance status (ECOG), n (%)							
0–1	271 (82.3%)	105 (96.3%)	166 (75.5%)	**<0.001**	173 (80.1%)	98 (86.7%)	0.170
2	58 (17.6%)	4 (3.7%)	54 (24.5%)		43 (19.9%)	15 (13.3%)	
T stage, n (%)							
1–2	80 (24.3%)	31 (28.4%)	49 (22.3%)	0.223	48 (22.2%)	32 (28.3%)	0.226
3–4	249 (75.7%)	78 (71.6%)	171 (77.7%)		168 (77.8%)	81 (71.7%)	
N stage, n (%)							
0–1	51 (15.5%)	18 (16.5%)	33 (15.0%)	0.747	30 (13.9%)	21 (18.6%)	0.266
2–3	278 (84.5%)	91 (83.5%)	187 (85.0%)		186 (86.1%)	92 (81.4%)	
Metastasis sites							
Brain	101 (30.7%)	70 (69.3%)	31 (30.7%)		59 (58.4%)	42 (41.6%)	
Bone	61 (18.5%)	42 (68.9%)	19 (31.1%)		41 (67.2%)	20 (32.8%)	
Pleura	89 (27.1%)	67 (75.3%)	22 (24.7%)		55 (61.8%)	34 (38.2%)	
Liver	220 (66.9%)	0 (0.0%)	220 (100%)		153 (69.5%)	67 (30.5%)	
Lung	92 (28.0%)	62 (67.4%)	30 (32.6%)		65 (70.7%)	27 (29.3%)	
Other sites	51 (15.5%)	29 (56.9%)	22 (43.1%)		27 (52.9%)	24 (47.1%)	
Number of hepatic metastases, n (%)							
≤3	141 (64.1%)				93 (61.2%)	48 (70.6%)	0.224
>3	79 (35.9%)				59 (38.8%)	20 (29.4%)	
EGFR mutation, n (%)							
Negative	216 (65.7%)	64 (58.7%)	152 (69.1%)	0.066			
Positive	113 (34.3%)	45 (41.3%)	68 (30.9%)				
Exon 19 deletion	69 (61.1%)						
Exon 21 mutation	44 (38.9%)						

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Table 2. Therapeutic effect in patients without hepatic metastases and with hepatic metastases.

		Without hepatic metastases		With hepatic metastases		P
Total, n (%)	SD+PR+CR	56	(51.4%)	87	(39.5%)	**0.045**
	PD	53	(48.6%)	133	(60.5%)	
Sex, n (%)						
Male	SD+PR+CR	28	(52.8%)	25	(21.7%)	**<0.001**
	PD	25	(47.2%)	90	(78.3%)	
Female	SD+PR+CR	28	(50.0%)	62	(59.0%)	0.318
	PD	28	(50.0%)	43	(41.0%)	
Age, n (%)						
<65	SD+PR+CR	35	(46.7%)	63	(35.8%)	0.121
	PD	40	(53.3%)	113	(64.2%)	
≥65	SD+PR+CR	21	(61.8%)	24	(54.5%)	0.645
	PD	13	(38.%)	20	(45.5%)	
Smoking, n (%)						
Smoker	SD+PR+CR	22	(51.4%)	26	(39.5%)	**0.004**
	PD	23	(48.6%)	84	(60.5%)	
Non-smoker	SD+PR+CR	34	(53.1%)	61	(55.5%)	0.875
	PD	30	(46.9%)	49	(44.5%)	
Performance status (ECOG), n (%)						
0–1	SD+PR+CR	53	(50.5%)	65	(39.2%)	0.079
	PD	52	(49.5%)	101	(60.8%)	
2	SD+PR+CR	3	(75.0%)	22	(40.7%)	0.305
	PD	1	(25.0%)	32	(59.3%)	
T stage, n (%)						
1–2	SD+PR+CR	20	(64.5%)	20	(40.8%)	0.066
	PD	11	(35.5%)	29	(59.2%)	
3–4	SD+PR+CR	36	(46.2%)	67	(39.2%)	0.333
	PD	42	(53.8%)	104	(60.8%)	
N stage, n (%)						
0–1	SD+PR+CR	10	(55.6%)	17	(51.5%)	1.000
	PD	8	(44.4%)	16	(48.5%)	
2–3	SD+PR+CR	46	(50.5%)	70	(37.4%)	**0.039**
	PD	45	(49.5%)	117	(62.6%)	
Number of hepatic metastases, n (%)						
≤3	SD+PR+CR			66	(46.8%)	**0.004**
	PD			75	(53.2%)	
>3	SD+PR+CR			21	(26.6%)	
	PD			58	(73.4%)	
EGFR mutation, n (%)						
Negative	SD+PR+CR	17	(26.6%)	52	(34.2%)	0.338
	PD	47	(73.4%)	100	(65.8%)	
Positive	SD+PR+CR	39	(86.7%)	35	(51.5%)	**<0.001**
	PD	6	(13.3%)	33	(48.5%)	

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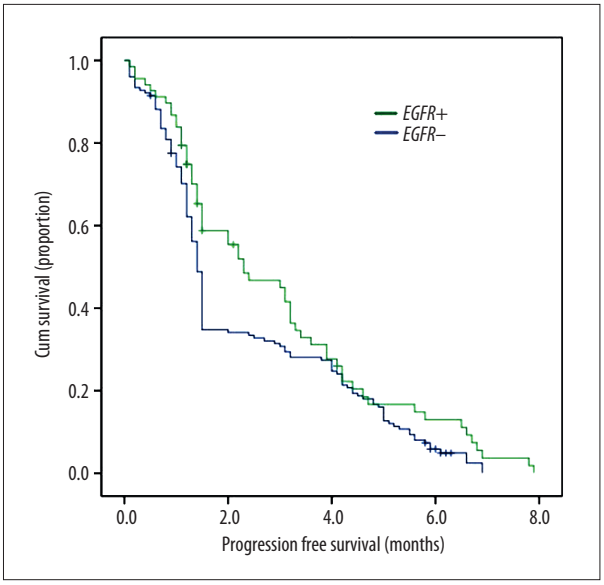

Figure 1. Association of *EGFR* Mutation and PFS in patients with hepatic metastases.

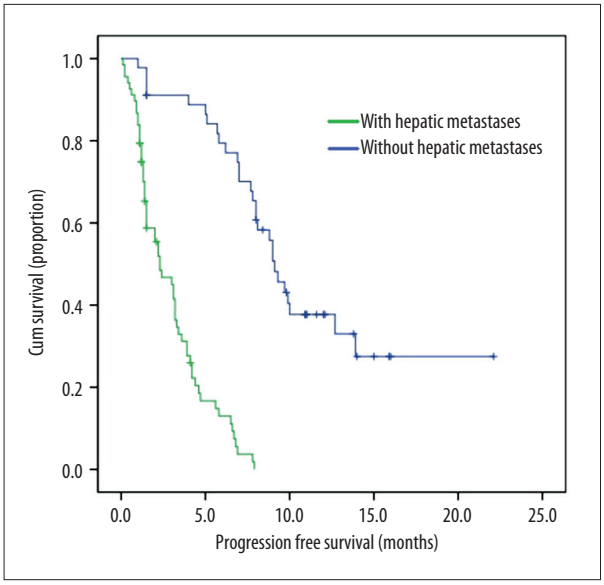

Figure 2. Association of hepatic metastases and PFS in patients with *EGFR* mutation.

Therapeutic effect

In the hepatic metastases group, the disease control rate was 39.5%, while in patients without hepatic metastases the disease control rate was 60.5% (P=0.045) (Table 2). In males (p<0.001), smokers (p=0.004), N2-3 (p=0.039), number of hepatic metastases >3 (p=0.004), and *EGFR*-positive (p<0.001) patients, the DCR rate was higher in patients without hepatic metastases than in patients with hepatic metastases.

Survival analysis

Median PFS in *EGFR* mutation-positive patients was 4.4 months and it was 1.4 months in *EGFR* mutation-negative patients (95% CI 2.799–6.001 *vs.* 1.329–1.471; P<0.001).

In patients with hepatic metastases, median PFS was 2.3 months in the *EGFR* mutation-positive group and 1.4 months in the *EGFR* mutation-negative (95% CI 1.314–3.286 *vs.* 1.325–1.475; P=0.055) (Figure 1).

In *EGFR* mutation-positive patients, median progression-free survival (PFS) was significantly longer in patients without hepatic metastases than in those with hepatic metastases (9.1 [95% CI 8.023–10.177] *vs.* 2.3 [1.314–3.286] months; P<0.001) (Figure 2).

Survival analysis in the whole population was performed (Table 3). The progression-free survival benefit seemed to be consistent across all clinical subgroups irrespective of sex, age, performance status, smoking status, T stage, N stage, number of hepatic metastases, or hepatic metastases status, suggesting that smoking status, *EGFR* mutations, and hepatic metastases are the most important factor in the PFS benefit in the whole population survival analysis.

Treatment-related adverse effects

The most frequent drug-related adverse effects were mild-to-moderate skin toxicity (56.1%) and diarrhea (55.3%) (Table 4). Liver toxicity was observed in more than 20% of patients without hepatic metastases. Dose reduction to 100 mg/d was necessary in 21 patients with hepatic metastases, due to increased alanine transaminase (ALT).

Discussion

The aim of our study was to investigate efficacy of erlotinib as 2nd/3rd line treatment in Chinese lung adenocarcinoma patients with hepatic metastases. We found that hepatic metastasis is a poor predictive marker for erlotinib in 2nd/3rd line treatment in patients with lung adenocarcinoma.

In advanced NSCLC, docetaxel or pemetrexed as the 2nd line chemotherapy can prolong survival after 1st line chemotherapy for NSCLC [6,7]. A study showed that in patients treated with docetaxel as 3rd line chemotherapy, survival was identical to that of patients treated with supportive care, but time to progression was longer for docetaxel patients than for best supportive care patients [6]. Erlotinib and gefitinib have been widely studied [23–37]. In phase II clinical trials of gefitinib [35,36], 10–20% of patients who received gefitinib after the 1st line therapy responded to gefitinib, and in a phase II

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Table 3. Survival analysis in the whole population.

	HR	P	95%CI
Sex (Male *vs.* Female)	1.087	0.703	0.709–1.665
Age (<65 *vs.* ≥65)	0.799	0.112	0.602–1.061
ECOG PS (0–1 *vs.* 2–3)	0.802	0.182	0.581–1.109
Smoking status (Yes *vs.* No)	0.605	**0.029**	0.385–0.949
T stage (1–2 *vs.* 3–4)	1.331	0.065	0.983–1.802
N stage (0–1 *vs.* 2–3)	0.807	0.220	0.572–1.137
Number of hepatic metastases (≤3 *vs.* >3)	0.860	0.359	0.622–1.188
EGFR mutation (No *vs.* Yes)	0.420	**<0.001**	0.311–0.566
Hepatic metastases (No *vs.* Yes)	1.830	**<0.001**	1.331–2.515

Table 4. Treatment-related adverse effects.

Toxicity, n (%)	Without hepatic metastases		With hepatic metastases		Total	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Neutropenia	3 (2.8%)	0 (0.0%)	17 (7.7%)	0 (0.0%)	20 (6.1%)	0 (0.0%)
Thrombocytopenia	2 (1.8%)	0 (0.0%)	15 (6.8%)	0 (0.0%)	17 (5.2%)	0 (0.0%)
Anemia	6 (5.5%)	0 (0.0%)	12 (5.5%)	5 (2.3%)	18 (5.5%)	5 (1.5%)
Infection	4 (3.7%)	0 (0.0%)	9 (4.1%)	0 (0.0%)	13 (4.0%)	0 (0.0%)
Skin rash	62 (56.9%)	2 (1.8%)	120 (54.5%)	4 (1.8%)	182 (56.1%)	6 (1.8%)
Diarrhea	32 (28.4%)	0 (0.0%)	62 (28.2%)	0 (0.0%)	94 (55.3%)	0 (0.0%)
Stomatitis	21 (29.4%)	0 (0.0%)	33 (15.0%)	0 (0.0%)	54 (17.7%)	0 (0.0%)
Paronychia	17 (15.6%)	0 (0.0%)	35 (15.0%)	0 (0.0%)	52 (16.4%)	0 (0.0%)
Vomiting or nausea	9 (8.3%)	0 (0.0%)	23 (10.5%)	0 (0.0%)	32 (9.7%)	0 (0.0%)
Increased ALT	25 (22.9%)	0 (0.0%)	77 (35.0%)	21 (9.5%)	102 (31.0%)	21 (6.4%)
Fatigue	15 (13.8%)	0 (0.0%)	37 (16.8%)	2 (1.0%)	52 (15.8%)	2 (0.06%)

clinical trial of erlotinib in previously treated NSCLC patients, the response rate was 12.3% [37]. These response rates are higher than with chemotherapy [6,7]. Clinical trials also demonstrated that erlotinib can prolong survival in previously treated NSCLC patients [11].

In our study, hepatic metastases were more common in the patients younger than 65 years old, and the PS of these patients were significantly higher. The DCR was 60.5% in patients without hepatic metastases, which is similar to results of a previous study [11]. However, the DCR and PFS in patients with hepatic metastases were lower than in patients without hepatic metastases. In males and smokers, N2–3, number of hepatic metastases >3, number of *EGFR*-positive patients, and DCR rate were significant higher in patients without hepatic metastases than in patients with hepatic metastases. In patients with hepatic metastases, PFS was not significantly different between the *EGFR* mutation-positive group and the *EGFR* mutation-negative group.

Lung cancer with EGFR-activating mutations responds favorably to the EGFR tyrosine kinase inhibitors gefitinib and erlotinib.

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However, many patients with EGFR-activating mutations show intrinsic resistance. In our research, DCR and PFS were lower in patients with hepatic metastases, perhaps because HGF, a ligand of *MET* oncoprotein, induces *EGFR* TKI resistance of lung adenocarcinoma cells with *EGFR*-activating mutations by restoring the phosphatidylinositol 3-kinase/Akt signaling pathway via phosphorylation of *MET*, but not *EGFR* or ErbB3 [14]. *MET* amplification activates ERBB3/PI3K/AKT signaling in *EGFR* mutant lung cancers, and causes resistance to *EGFR* kinase inhibitors. *MET* activation by its ligand, HGF, also induces drug resistance, but through GAB1 signaling [15]. We should also consider the possibility that the actual status of *EGFR* genes in hepatic metastases could be different from the status of the tumor sample analyzed. The samples used for *EGFR* gene analysis in this study were derived from lung tumors before initiation of chemotherapy, not from liver tumors, and all the patients had received 1 or 2 prior chemotherapy regimens. Previous research suggests that the *EGFR* mutation status changes after chemotherapy [39]. All the above-mentioned factors may influence the efficacy of erlotinib and may cause poor curative effect of erlotinib in the liver.

Erlotinib was well tolerated in our study. The most common toxicities are rash and diarrhea in patents without hepatic metastases. Patient response was primarily correlated with the grade of rash, consistent with results of several other trials [11]. Patients who had hepatic metastases had much higher ALT levels after taking *EGFR*-TKIs. Hepatic function should receive more attention in patients with hepatic metastases.

Our study has some limitations which should be taken into consideration. Firstly, this was a retrospective study. Secondly, the patients in our study came from a single center.

Conclusions

We found that hepatic metastasis is a poor predictive marker for erlotinib as 2nd/3rd line treatment in patients with lung adenocarcinoma. Combination therapy, for example with *MET*-TKI, may be a good choice for patients with liver metastases with poor prognosis. Further research is needed to explore the overall survival between patients with hepatic metastases and patients without hepatic metastases.

Conflict of interest statement

There are no conflicts of interest.

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