RESEARCH ARTICLE

Impaired Liver Function Implied Shorter Progression Free Survival for EGFR Tyrosine Kinase Inhibitors

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Abstract

Background: Epithelial growth factor receptor tyrosine kinase inhibitor (EGFR TKI) revolutionize the standard of care for advanced non-small cell lung cancer (NSCLC) harboring sensitive EGFR mutation. Liver toxicity is the dose-limiting factor for TKI but its importance is largely overlooked. Here the relationship between the elevation of transaminase and progression-free survival (PFS) was explored. **Methods:** This was a retrospective study where patients with advanced NSCLC were screened. And those treatment-naïve and with sensitive EGFR mutation who were prescribed with EGFR TKI were enrolled. The highest level of transaminase (alanine aminotransferase, ALT, and aspartate transaminase, AST) during the treatment course was recorded. **Results:** Totally 208 patients were recruited, and most of them (48.6%) took gefitinib. The whole cohort achieved a median PFS of 11.2 months (95%CI: 10.0-12.3 m). 73 (35.1%) patients had elevated transaminase and most was attributed to gefitinib (n=43, 42.5%). Specifically, ALT was elevated in 65 patients (31.3%) while AST in 24 patients (11.5%). Again, gefitinib was associated with more cases of ALT (40.6%) and AST (17.8%) elevation. The elevation of AST was not related to PFS (P=0.259, HR=0.751, 95%CI: 0.464-1.214). Interestingly, those with normal ALT level had a longer PFS (12.6m, 95%CI: 10.6-14.5 m) than those with elevated ALT (9.5m 95%CI: 7.9-11.0 m, P=0.025, HR=0.682, 95%CI: 0.488-0.953). The inverse relationship was confirmed in the COX regression analysis (P=0.047). **Conclusion:** This study revealed the side effects of elevated ALT was inversely related to the PFS of EGFR TKI treatment. The liver impairment by TKI should not be overlooked.

Keywords: Epithelial growth factor receptor (EGFR)- lung cancer (NSCLC)-progression-free survival (PFS)

Introduction

Lung cancer ranks first both in morbidity and mortality in malignancies (Siegel et al., 2017). 80% of lung cancer cases are non-small cell lung cancer. More than half of the patients are diagnosed at an advanced stage of the disease, with median overall survival (OS) of merely 10-12 months when standard platinum-base chemotherapy is given (Hirsch et al., 2017). Targeted therapy revolutionized the standard of care for the patients with tumors harboring epithelial growth factor receptor (EGFR) mutation, and achieved a median progression-free survival (PFS) of 8-10 months and an objective response rate (ORR) of about 70%. However, even though patients responded favorably to targeted therapy, the effects varied among patients, and PFS lasted for months to years. This definitely implied factors might contribute to the TKI therapeutic effects.

Although often overlooked, elevated hepatic transaminase was a dose-limiting toxicity for EGFR tyrosine kinase inhibitors (TKI), esp. for gefitinib. In previous series of reports, elevated transaminase occurred in about 10% of patients prescribed with gefitinib (Ranson et al., 2002). In addition, those achieved a good control of their tumors by gefitinib with elevated transaminase composed a challenge in clinical settings (Seki et al., 2006; Takeda et al., 2010). However, the impact of elevated transaminase on the therapeutic effects remains unknown. This study explored the relationship between PFS after TKI treatment and the level of transaminase.

Materials and Methods

Patients

This was a retrospective study conducted in West China Hospital (a tertiary referral center) from October 2013 to October 2016. To be enrolled, patients must have pathological confirmed NSCLC, older than 18 years, ECOG performance of 0 or 1, and have metastatic diseases (stage IV, according to the American Joint Committee On Cancer Stage Manual, the seventh edition). They were treatment-naïve, and prescribed with EGFR TKI. But those with concomitant other cancer were excluded. In addition, patients who took drugs significantly affecting liver function were excluded. The clinical data were retrieved through a pre-established database, which was an infrastructure of the National Major Project of China

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(2011ZX09302-001-01, Li et al., 2015). The ethical committee of Sichuan University reviewed the study concept and the study was performed in accordance with the Declaration of Helsinki.

Drugs

Gefitinib (Irressa, AstraZeneca, UK), erlotinib (Tarceva, Roche, Switzerland), and icotinib (Conmana, Beta, China) were all first generation EGFR TKIs, and they had comparable efficacy (Shi et al., 2013; Utara et al., 2016). The prescription of the TKI was up to the treating physician discretion. Both gefitinib and erlotinib were taken once per day, while icotinib was orally medicated three times a day. The tumor response was monitored by radiographic examinations including chest and abdominal enhanced computed tomography, brain magnetic resonance imaging, and bone single-photon emission computed tomography regularly. The response was assessed by the treating physician according to the Response Evaluation Criteria in Solid Tumor 1.1 criteria (Eisenhauer et al., 2009). The interruption or switch of TKI was decided by the treating physicians.

EGFR mutation status

All the patients had their tumor EGFR gene mutation detected before taking TKI. Genetic testing was performed by ARMS using a commercially available kit (AmoyDx, Shameng, China) in a College of American Pathologists (CAP)-certified lab in West China Hospital. The detection method is under the authorization of the Chinese Food and Drug Administration. Briefly, tissue blocks were sliced into 5 μm sections, and tumor content was assessed by board-certified pathologists using hematoxylin and eosin staining. All specimens contained more than 10% of tumor content. DNA was extracted using the QIAamp DNA mini kit (Qiagen).

Liver function assay

The biochemical profile of the blood from the patients were monitored regularly during the course of TKI administration at an interval of 1 week. The liver function assay was performed on an automatic biochemical analyzer (Roche Cobas8000) in the CAP-certified lab. The highest level of transaminase during the treatment course was recorded. The level above the upper limit of normal reference (ALT≤50, AST≤45) was considered elevated.

Statistical analysis

All statistical analysis was conducted with SPSS 19.0 (IBM Inc., Chicago, IL). PFS was defined as the duration of time between the TKI treatment and the first sign of disease progression. Student's t and Chi-square test were used for continuous and categorical variables separately. Survival analysis was performed by the Kaplan-Meier method. Multivariate analysis was performed by Cox regression model Variables with P < 0.1 in univariate analysis were considered into multivariate analysis. A two-side P-value less than 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 208 patients were enrolled in this study. The baseline demographic characteristics were shown in Table 1. In summary, most of them were non-smokers (n=147, 70.7%), and had adenocarcinoma (n=194, 93.3%). The median age was 59.5 year (range: 31-85). Female gender (n=116, 55.8%), EGFR exon 19 deletion (19Del, n=113, 54.8%), and gefitinib-taken (n=101, 48.6%) were composed roughly half of the population.

Table 1. Demographic Features of the Patients

Characteristic	N	%
Sex		
Male	92	44.2
Female	116	55.8
Age (years)		
Median	59.5	
Range	31-85	
Smoking History		
Yes	61	29.3
No	147	70.7
Histological Type		
Adecarcinoma	194	93.3
Non- Adecarcinoma	14	6.4
EGFR-mutation type		
19DEL	113	54.8
L858R	80	38.7
Others	15	6.5
TKI		
Gefitinib	101	48.6
Icotinib	76	36.5
Erlotinib	31	13.9

Table 2. COX Multivariate Regression Analysis

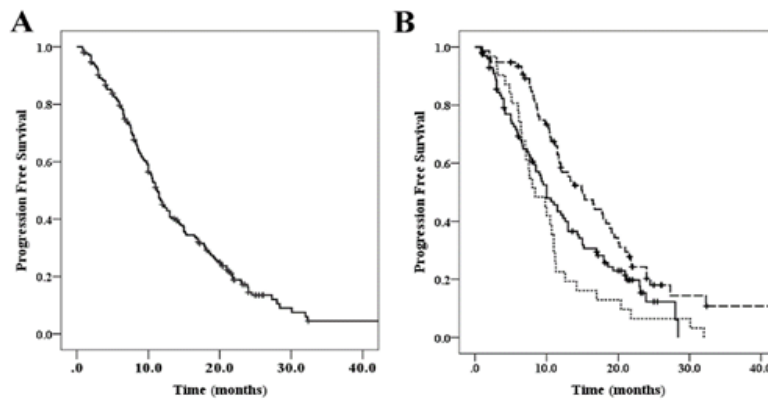|	HR	95%CI	P
ALT			
Elevated			
Normal	0.699	0.492-0.995	0.047
Smoking			
Non-smoker			
Smoker	1.005	0.611-1.651	0.985
Age			
>60 years			
≤60 years	0.985	0.705-1.374	0.927
Gender			
Male			
Female	1.547	0.983-2.435	0.059
Mutation			
Exon19Del			
others	1.092	0.838-1.425	0.514

Figure 1. PFS of the Whole Cohort (A) and the Gefitinib (Solid Line), Erlotinib (Dotted Line), and Icotinib (Dash Line, B).
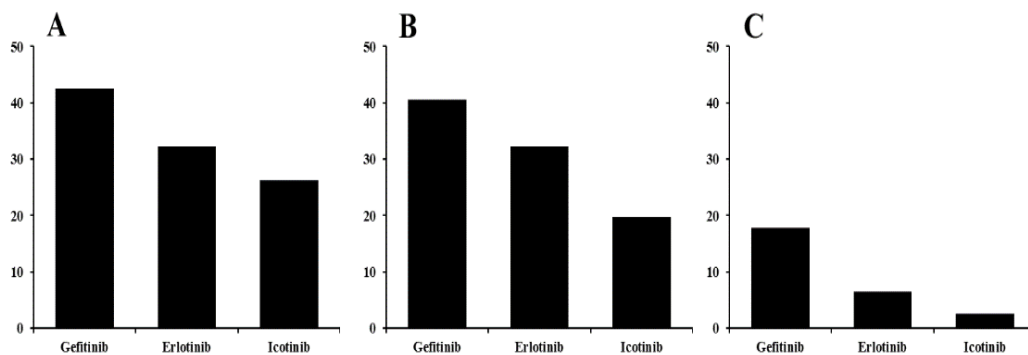

Figure 2. Prevalence of Elevated Transaminase (A), ALT (B), and AST (C) in Gefitinib, Erlotinib, and Icotinib Respectively

Treatment and efficacy

101 (48.6%), 31 (13.9%), and 76 (36.5%) patients took gefitinib, erlotinib, and icotinib respectively. The whole cohort achieved a median PFS of 11.2 months (95%CI: 10.0-12.3 m). The PFS was 10.0 m (95%CI: 7.9-12.0 m), 8.4 m (95%CI: 5.6-11.1 m), 15.0 m (95%CI: 11.0-18.9 m) for gefitinib, erlotinib, and icotinib respectively. Icotinib seemed to have longer PFS among the three (P=0.001, Figure 1). However the comparison was not definitive due to the possible sampling bias.

Transaminase

During the treatment course, 73 (35.1%) patients had elevated transaminase. Most were attributed to gefitinib (n=43, 42.5%), and less to erlotinib (n=10, 32.3%), or icotinib (n=20, 26.3%). Specifically, the elevation of alanine aminotransferase (ALT, 31.3%) was more prominent than aspartate transaminase (AST, 11.5%). Gefitinib was associated with more cases of ALT (n=41, 40.6%) than erlotinib (n=10, 32.2%) and icotinib (n=15, 19.7%). The same trend was observed for AST, more patients was affected by gefitinib (n=18, 17.8%) than erlotinib (n=2, 6.5%) or icotinib (n=2, 2.6%, Figure 2).

To rule out the impact of HBV infection, the HBV serotyping was collected and analyzed. 77.4% (n=161) of the cohort had the HBV serotyping assayed, and among them 75.1% (n=124) were found to be positive of HBV surface antigen (HBsAg). However this study found the
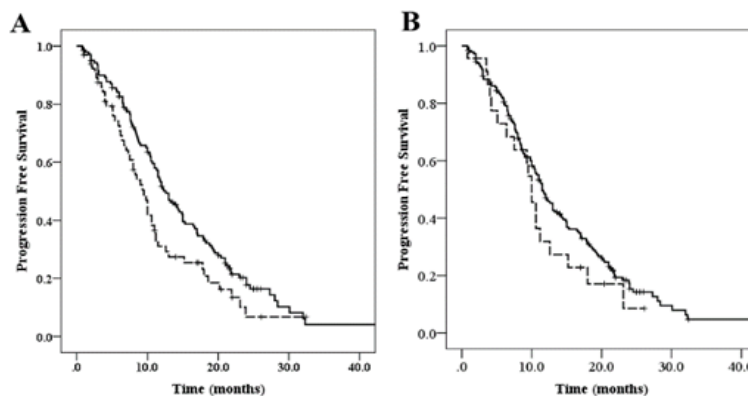

Figure 3. PFS of Normal (Solid Line) and Elevated (Dash Line) ALT (A) and AST (B).

elevation of transaminase was unrelated to the HBV infection by Chi-square analysis (P=0.153). In addition, our study found none of our patients had relapsed HBV during the treatment course.

Although patients had impaired liver function, few of them (n=2, 0.9%) had TKI therapy interrupted. And the two patients continued TKI after recovery of transaminase level and remained normal thereafter.

PFS and transaminase

The relationship between PFS and transaminase was explored. Patients with (10.0m, 95%CI: 8.8-11.1m) or without (11.5m, 95%CI: 10.1-12.8m) elevated AST had similar PFS (P=0.259, HR=0.751, 95%CI: 0.464-1.214), while interestingly an inverse correlation was found between PFS and ALT level. Those with normal ALT level had a longer PFS (12.6m, 95%CI: 10.6-14.5 m) than those with elevated ALT (9.5m 95%CI: 7.9-11.0 m, P=0.025, HR=0.682, 95%CI: 0.488-0.953, Figure 3). Additionally, in our multivariate COX regression model, ALT was found to be an independent factor after adjusting age, gender, mutation, and smoking status (P=0.047, Table 2).

Discussion

In this retrospective study, a cohort of 208 patients with metastatic NSCLC who were prescribed with first-line EGFR TKI was enrolled. We found the high prevalence of elevated transaminase among the patients, esp. for the patients with gefitinib. Although impaired liver function frequently presented, none of this cohort of patients had relapsed HBV hepatitis. Elevated ALT was more frequently observed than AST. In addition, an inverse correlation between ALT but not AST elevation and PFS was observed. Those with elevated ALT tended to have longer PFS.

Liver impairment was largely underappreciated in clinical practice although it was the dose-limiting toxicity for gefitinib. In large-scale phase III trials, severe liver impairment occurred in about 20% patients receiving gefitinib (Mitsudomi et al., 2010; Maemondo et al., 2010). Given good tumor control, abruption of TKI after severe liver impairment was a dilemma for clinicians, and various strategies were reported (Seki et al., 2006; Takeda et al., 2010). This study explored the relationship between the extent of liver impairment and PFS, and found they were inversely related. To our best knowledge, few reports were on this association before out study. Our study provided new insights into the in vivo effects of TKI treatment.

Although ALT and AST were both transaminase, reflecting the extent of liver impairment, they were subtly varied in their distribution and response to liver insult. ALT mainly located in the cytoplasm of hepatocytes, and release of ALT into blood was considered an acute consequence of cell membrane damage. In contrast, AST was restricted in the cellular organelle such as mitochondria, and elevation of plasma AST was commonly subjected to chronic and culminate liver damage. In this study, TKI was found to impact ALT level more extensively than AST. This might imply hepatocytes

impairment by TKI was mild and not as severely as that by hepatitis virus.

Medication of gefitinib was associated with more patients with liver impairments than the other two, although they had similar tumor control effects. This was supported by other previous reports as well (Shi et al., 2013; Urata et al., 2016). The mechanism underlying might be related the different modification of the side-chain modification of quinazolin cycle. Both gefitinib and erlotinib were metabolized in liver by cytochrome P450 (CYP) enzymes (CYP3As), but they were preferentially metabolized by CYP2D6 and CYP1A2 respectively (Li et al., 2007). Gefitinib probably bound with high affinity to hepatocytes and led to transaminase release thereafter.

It was elusive why the elevated ALT level was correlated inversely to the PFS for TKI treatment. Most possibly, the intra and extra- hepatic CYP enzymes activities were correlated. Impaired liver function might suggest the low-efficiency of intrahepatic CYP enzymes and accumulation of TKIs, and reduced TKI level in circulation and tumor cells as a sequence. Also, cancer cells stemmed from normal cells, and they might carry similar characteristics to normal cells. To some extent, low tolerance to TKI of hepatocytes reflected the nature of insensitivity of tumor cells to TKI. Alternatively, impaired liver function might imply the lower plasma concentration of TKI, and worse EGFR inhibition thereafter. After all, the underlying mechanistic explanation need to be further explored.

In this study, none of the patients in this cohort developed relapsed HBV hepatitis during the course of TKI treatment. This contrasted sharply to that of chemotherapy, where HBV reactivation was common in about 20% patients, even at the face of lamivudine protection (about 10%, Lin et al., 2014). We also reported a small-cell lung cancer case with fulminant HBV hepatitis after chemotherapy (Qin et al., 2016). The difference might be due to the immune inhibition of chemotherapy, but this also argued for the favorite safety of TKI compared with chemotherapy.

The current study had its limitations. The study was based on a relatively small sample size, performed retrospectively in a single institute. The selection bias was always inevitable. However this was an exploratory study and provided novel clues to the prognosis of patients with TKI treatments, and was not intended to change the paradigm of clinical practice. If appropriate, the conclusion need to be confirmed in prospectively designed clinical trials. Secondly, this study suggested liver impairment impacted negatively to the effects of TKI, while no in vivo direct interaction was shown here. Thirdly, in real world practice, surrogate markers such as transaminase variation during the treatment course were hardly be monitored regularly.

This study summarized the transaminase profile in patients received TKI treatment. We found TKI treatment extensively influenced the liver function, esp. for patients prescribed with gefitinib. TKI treatment led to no hepatitis virus relapse. Most interestingly, the elevation of ALT but not AST was inversely related to the PFS of treatment.

This study both provided a potential biomarker and suggested complex in vivo interaction with liver for TKI.

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