Observation of hepatotoxicity during long-term gefitinib administration in patients with non-small-cell lung cancer

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To observe drug-induced hepatotoxicity by long-term gefitinib administration in the treatment of non-small-cell lung cancer. The data of 101 patients with locally advanced or metastatic non-small-cell lung cancer, for which gefitinib had been used orally for 3 months or longer, were retrospectively analyzed. The median duration of gefitinib administration was 14 months (3–60 months). Forty patients (39.6%) developed abnormal hepatic function, among whom 30 patients (29.7%) had grade I hepatotoxicity, six patients (5.9%) had grade II, and four patients (4.0%) had grade III, respectively. The median time from starting gefitinib oral therapy to developing liver dysfunction was 4 months (1–23 months) for the entire cohort. The incidence of hepatotoxicity in the group with a duration of more than 14 months was much higher than that in the group with a duration of less than 14 months (52.0 vs. 27.5%, $P = 0.012$). In thirty-two patients (32/40), abnormal liver function resolved with hepatoprotective treatment, whereas eight patients (8/40) had persistent grade I hepatotoxicity until the last follow-up. Our study showed that long-term gefitinib-induced hepatotoxicity was a common adverse event, especially for the cohort with a duration of longer than 14 months. In most patients with hepatotoxicity, normal liver function was restored and discontinuation of gefitinib was not necessary. ***Anti-Cancer Drugs*** **27:245–250** **Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.**

Anti-Cancer Drugs 2016, **27**:245–250

Keywords: gefitinib, hepatotoxicity, non-small-cell lung cancer

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Received 8 October 2015 **Revised form accepted** 5 November 2015

Introduction

Non-small-cell lung cancer (NSCLC) accounts for ~80% of all lung cancers [1] and 50–60% of newly diagnosed patients have locally advanced or metastatic disease [2]. The long-term survival rate of patients with locally advanced and metastatic NSCLC varies by disease characteristics, but is generally low, with 5-year survival rates for stages IIIA, IIIB, and IV being 8–14, 1–5, and 1–5%, respectively [3–6]. The discovery of activating mutations of the epidermal growth factor receptor (*EGFR*) gene and the clinical application of *EGFR*-tyrosine kinase inhibitors such as gefitinib and erlotinib have provided another choice and a new treatment pattern for advanced NSCLC [7–14]. Two recent randomized studies (NEJ002 and WJTOG3405) have shown that the progression-free survival of patients treated with gefitinib is longer than that of patients treated with platinum doublets in the first-line treatment for advanced NSCLC harboring activating *EGFR* mutations [9,10]. The commonly reported adverse effects of gefitinib include skin rash (71–85%) and diarrhea (34–54%), but less attention has been paid to gefitinib-induced hepatotoxicity; in particular, there is little published data available on hepatotoxicity induced by long-term gefitinib oral therapy outside clinical trial settings. Our study thus retrospectively analyzed clinical data from 101 patients with a history of long-term gefitinib administration and their liver toxicity profiles.

Patients and methods

Patients

From January 2009 to January 2013, the data of 337 patients who presented to the Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College with a history of oral gefitinib administration were collected. The eligibility criteria for this study were as follows: (a) age greater than 18 years; (b) histologically or cytologically confirmed NSCLC; (c) imaging-confirmed locally advanced (stages IIIA and IIIB) or metastatic NSCLC (stage IV); (d) oral gefitinib therapy for 3 months or longer duration and available laboratory data; and (e) WHO performance status of 0–2. In addition, patients with asymptomatic brain metastases were also included. The exclusion criteria were as follows: (a) less than 3 months of gefitinib administration; (b) liver dysfunction or diagnosed with hepatometastasis before gefitinib therapy; and (c) concurrent chemotherapy with gefitinib or systemic anticancer therapy within

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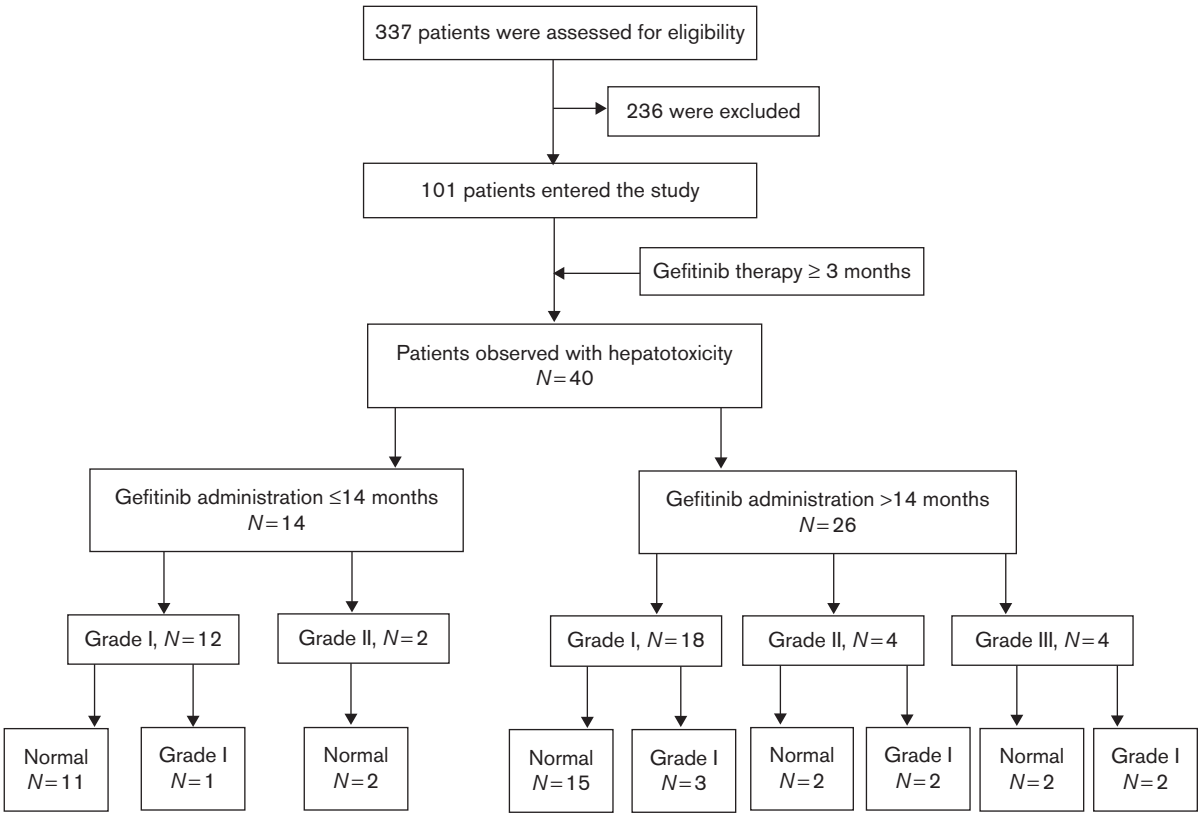
DOI: 10.1097/CAD.0000000000000323

Fig. 1



Screening, gefitinib administration, incidence of hepatotoxicity, and recovery. The duration of gefitinib administration was used to divide two subgroups with a 14-month cut-off.

21 days before gefitinib administration. Finally, 101 of 337 patients were included in this study (Fig. 1).

Gefitinib therapy and laboratory assessments

Gefitinib was administered orally at the standard dose of 250 mg per day. Liver function was examined regularly at the first, third, fifth, and seventh months from initiation of gefitinib therapy and a follow-up by every 2–3 months afterwards. Hepatitis B virus surface antigen and hepatitis C virus serology were performed for all patients at the baseline visit. Liver toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 3.0 by the National Cancer Institute of America. It defines grade I, grade II, grade III, and grade IV toxicity levels of alanine transaminase, aspartate aminotransferase, and alkaline phosphatase (ALP) as 1.0–2.5 times, 2.5–5.0 times, 5–10 times, and more than 10 times the upper limit of normal (ULN), respectively. Increases in total bilirubin levels of 1.0–1.5 times, 1.5–2.5 times, 2.5–5.0 times, and more than five times the ULN are defined as grade I, grade II, grade III, and grade IV toxicity, respectively. Grade I and grade II hepatotoxicity is defined as mild hepatotoxicity, whereas grade III and higher grade toxicities are defined as severe.

Management of hepatotoxicity

Once liver injury was identified, liver protection therapy would be administered to patients, including glycyrrhizic, reduced glutathione, polyene phosphatidyl choline, ademetionine 1, 4-butanedisulfonate, vitamin, and coenzyme. In this study, patients with mild hepatotoxicity were continued on gefitinib therapy. Resolutions included hepatoprotective medicine, reducing concurrent medication (such as traditional Chinese medicine, immunity-improving medicine, antibiotics, and cold medicine), and intensive monitoring. Patients with severe hepatotoxicity, in contrast, discontinued their gefitinib regimen until their liver function recovered to grade I or normal level after hepatoprotective medication. In addition, gefitinib therapy was discontinued with the occurrence of any grade 4 nonhematologic toxicities.

Statistical analysis

All patients were monitored from the initiation of gefitinib therapy through their last follow-up visit up to 12 weeks after discontinuation of gefitinib. The time of development of liver dysfunction during gefitinib administration was defined as the period from the date of starting gefitinib to the time of hepatotoxicity detected.

The duration of gefitinib administration was used to divide two subgroups with a 14-month cut-off. Pearson χ^2 or Fisher's exact tests were used to compare clinicopathologic variables and the incidences of liver dysfunction between these two subgroups.

Results

Patient characteristics

One hundred and one patients comprised the population of this study. Sixty-three patients were women and 38 were men, median age 60 years (36–85 years). Coexistent conditions included fatty liver steatosis ($N=6$), positive hepatitis B virus surface antigen ($N=5$), cardiovascular diseases or diabetes mellitus ($N=38$), and other diseases ($N=6$). During the gefitinib therapy, patients were on concurrent medications; 42 patients (41.6%) were on monthly intravenous bisphosphonate, 23 (22.8%) were on cardiovascular or diabetes-related drugs, 17 (16.8%) were taking traditional Chinese medicine, 17 (16.8%) were taking immunity-improving medicine (including thymosin, ubenimex), 11 patients (10.9%) were on analgesics (including acetaminophen, diclofenac sodium, oxycodone, or morphine), and eight patients (7.9%) were on other medications (including antibiotic or cold medicine) (Table 1). Baseline characteristics of the two groups on the basis of the duration of gefitinib administration (≤ 14 vs. >14 months) are listed in Table 2.

Incidence of hepatotoxicity and time of development of hepatotoxicity

The median duration of gefitinib therapy was 14 months (3–60 months) and the median follow-up duration was 17 months (6–63 months). During gefitinib administration and follow-up, 40 patients (39.6%) developed abnormal hepatic function (Table 3). An increase in aminotransferase was the most common gefitinib-induced liver abnormality (28.7%). An increase in total bilirubin elevation was observed in 10 patients (9.9%). A simultaneous increase in both direct and indirect bilirubin was most common (5/10), with exclusive direct increase in bilirubin in two patients and exclusive indirect increase in bilirubin in three patients. No grade 4 hepatotoxicity was observed in this group of patients. Overall, the median time of observation of liver dysfunction from gefitinib administration was 4 months (1–23 months). The median time for development of grade I, II, and III hepatotoxicity was 5 (1–23 months), 3.5 (2–8 months), and 2.5 (1–5 months) months, respectively.

Table 1 Patient characteristics

	N (%)
Age	60 (36–85)
Sex	
Female	63 (62.4)
Male	38 (37.6)
Therapy status	
First-line	17 (16.8)
≥ Second-line	84 (83.2)
Pathological type	
Adenocarcinoma	95 (94.1)
Other types	6 (5.9)
EGFR mutation	
Positive	45 (44.6)
Unknown	56 (55.4)
Complication	
Fatty liver steatosis	6 (5.9)
Positive hepatitis B surface antigen	5 (5.0)
Cardiocerebrovascular diseases or diabetes mellitus	38 (37.6)
Others	6 (5.9)
Concurrent medication	
Bisphosphonate	42 (41.6)
Cardiocerebrovascular or diabetes-related drugs	23 (22.8)
Traditional Chinese medicine	17 (16.8)
Immunity-improving medicine	17 (16.8)
Analgesics	11 (10.9)
Others	8 (7.9)

EGFR, epidermal growth factor receptor.

Table 2 Baseline characteristics on the basis of the duration of gefitinib administration

	N (%)		
Clinical factors	Duration ≤ 14 months (*N* = 50)	Duration > 14 months (*N* = 51)	*P*
Age			
≤ 60	28 (56)	23 (45)	0.273
> 60	22 (44)	28 (55)	
Sex			
Female	33 (66)	30 (59)	0.457
Male	17 (34)	21 (41)	
Stage			
III	12 (24)	10 (20)	0.593
IV	38 (76)	41 (80)	
Therapy status			
First-line	7 (14)	10 (20)	0.451
≥ Second-line	43 (86)	41 (80)	
Brain metastasis			
Yes	3 (6)	5 (10)	0.479
No	47 (94)	46 (90)	
EGFR mutation			
Exon 19 deletion	9 (18)	18 (35)	0.004
L858R	5 (10)	13 (25)	
Unknown	36 (72)	20 (39)	
Concurrent medication			
Yes	39 (78)	31 (61)	0.061
No	11 (22)	20 (39)	
Complicated liver disease			
Yes	6 (12)	5 (10)	0.723
No	44 (88)	46 (90)	

EGFR, epidermal growth factor receptor.

Table 3 Forty patients with various grades of hepatotoxicity (without grade IV hepatotoxicity)

	N (%)			
Grade of hepatotoxicity	I	II	III	Total
ALT/AST elevation	21[a] (20.8)	4 (4.0)	4[b] (4.0)	29 (28.7)
ALP elevation	3[a] (3.0)	0	0	3 (3.0)
TBIL elevation	7 (6.9)	3[b] (3.0)	0	10 (9.9)
Total	30 (29.7)	6 (5.9)	4 (4.0)	40 (39.6)

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; TBIL, total bilirubin.

[a]One patient diagnosed of both grade I ALT/AST elevation and grade I ALP elevation was classified into grade I hepatotoxicity.

[b]One patient diagnosed of both grade III ALT/AST elevation and grade II TBIL elevation was classified into grade III hepatotoxicity.

Analyses of hepatotoxicity with different grades

Mild (grade I and II) hepatotoxicity: 36 patients (35.6%) presented mild hepatotoxicity, 30 (29.7%) grade I and six (5.9%) grade II. Elevated aminotransferase (25/36) was most frequently observed, followed by increased bilirubin (9/36) and ALP (3/36) (Table 3). In patients with elevated bilirubin, an increase in both direct and indirect bilirubin was observed in four of nine patients. Coexistent hepatic conditions included two patients with fatty liver steatosis and three patients with positive hepatitis B virus surface antigen. Only one out of 36 patients discontinued gefitinib therapy and concurrent medication because of hepatotoxicity and after 3 weeks of hepatoprotective treatment, his hepatotoxicity grade decreased from grade II to grade I, and then he resumed the treatment of gefitinib 250 mg daily without comedication and continued liver protection treatment. Up to the last follow-up, recurrent hepatotoxicity had not been observed.

Severe (grade III) hepatotoxicity: Four patients (4.0%) developed grade III hepatotoxicity, all of whom (4/4) presented with elevated aminotransferase, with one patient showing a simultaneous increase in both direct and indirect bilirubin. One patient had coexistent fatty liver steatosis. Three out of the four patients discontinued the gefitinib regimen and concurrent medication. After 2–4 weeks of hepatoprotective treatment and a re-examined liver function test recovered to grade I liver injury, all three patients were rechallenged with gefitinib 250 mg/day. The other patient continued gefitinib therapy despite the hepatotoxicity, but stopped her concurrent medication (traditional Chinese medicine), and her liver function recovered after 1 week.

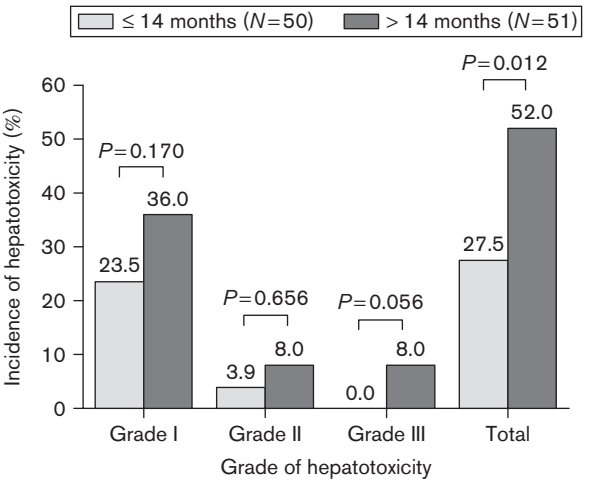
Effect of gefitinib administration duration on hepatotoxicity

The median duration of gefitinib administration (14 months) was considered a cut-off. The incidence of hepatotoxicity in the group with a duration of less than 14 months of therapy was much lower than that in the group of patients receiving gefitinib therapy for more than 14 months (27.5 vs. 52.0%, $P = 0.012$). Similar trends were observed across grade I, II, and III hepatotoxicity groups, but the difference did not reach statistical significance (Fig. 2).

Treatment and recovery of hepatotoxicity

The combination of two hepatoprotective drugs was the common regimen and the duration of medication varied from 1 week to 3 months. Liver function was re-examined every 1 or 2 weeks until liver function became normal. In 32 patients (32/40, 80%), liver function recovered, whereas 8 (8/40, 20%) still presented grade 1 hepatotoxicity at the end of follow-up (Fig. 1). Four patients discontinued gefitinib therapy because of hepatotoxicity: one in the mild hepatotoxicity group and three in the severe hepatotoxicity group. Discontinuation of concurrent medications was observed in 15 patients.

Fig. 2



Difference in the incidence of hepatotoxicity in the group with a duration of less than 14 months of therapy and the group with a duration of more than 14 months of therapy.

Discussion

Over 1000 drugs have been reported capable of inducing acute or chronic liver injury [15]. The results of our study suggested that hepatotoxicity was a common adverse event during the long-term oral administration of gefitinib. The majority showed an increase in aminotransferase (28.7%), mostly a mild increase (24.7%), followed by an increase in bilirubin (9.9%) and an increase in ALP (3.0%).

An increase in aminotransferase is the most common laboratory evidence of gefitinib-induced liver injury. A severe gefitinib-induced increase in aminotransferase has been reported in up to 9.4% of patients with grade III or worse in Asia [12]. However, data from a Japanese study tended to be much higher. Patients with higher than grade III abnormal aminotransferase reported by ENJ002 and EJTOG3405 were 26.3 and 24%, respectively [9,10]. In our study, 28.7% of patients were diagnosed with elevated aminotransferase and only four patients (4.0%) were grade III. It is difficult to compare the differences in the incidence of hepatotoxicity in various researches because of the different time points of detection of liver function and heterogeneity in patient populations. In addition, ALP or bilirubin elevation was rarely reported, whereas in our study, 3.0% of patients presented with elevated ALP and in 9.9% of patients, an increase in bilirubin (mostly a simultaneous increase in both direct and indirect bilirubin) was observed. The results suggested that gefitinib may also induce an increase in bilirubin by impairing hepatocyte.

There are limited data on the time period of development of liver injury during gefitinib administration. In one case report, the patient presented with significantly increased aminotransferase after 8 weeks of gefitinib therapy and the liver function recovered to normal after 2 months [16]. In our study, patients developed liver injury in 1–23 months (median time 4 months) and the median time of development of grade I, II, and III hepatotoxicity was 5, 3.5, and 2.5 months, which indicates that severe liver injury tends to present in the early stage of gefitinib administration. The results were consistent with that of the Japanese research, in which most of the adverse events were recorded in 3 months [17].

To our knowledge, there has been no research suggesting that the incidence of hepatotoxicity increased with an increase in the duration of gefitinib administration. In our study, the incidence of hepatotoxicity in the group with a duration of more than 14 months of therapy was much higher than that in the group with less than 14 months of therapy (52.0 vs. 27.5%, $P = 0.012$). The mechanism for such result is not well known. CYP2D6 catalyzed gefitinib into ortho-desmethyl-gefitinib, the major metabolite observed in human plasma [18]. Takimoto *et al.* [19] reported that the reduced function of CYP2D6 may partly account for gefitinib-induced hepatotoxicity when CYP3A4 is inhibited. In addition, there are several reports showing the relation between the CYP2D6 genotype and gefitinib clearance. Geometric mean area under the curve and peak plasma concentration of gefitinib were higher in poor CYP2D6 metabolizers compared with extensive metabolizers [20,21]. Therefore, in patients with a genetic background of dysfunctional CYP2D6, decreased activity might lead to severe overdose of gefitinib and consequently an increase in the incidence of gefitinib-induced hepatotoxicity. However, the activity of CYP2D6 was not known in this study because of the retrospective nature of the research. Therefore, further studies are warranted to determine the mechanism clearly. Our study suggests that the liver function of patients with long-term administration of gefitinib should be monitored closely.

Several previous studies have investigated other factors affecting gefitinib-induced hepatotoxicity and the results suggested that the liver injury of gefitinib may be dose dependent as it had been observed in a multicenter phase II trial with advanced-stage NSCLC. The incidence of patients developing grade I or II hepatotoxicity was 10.7 and 17.9% when receiving gefitinib at a dose of 250 and 500 mg/day, respectively [22]. Previous researches also showed that the hepatitis B virus could be a potential risk factor for development of drug-induced toxicity [23]. This conclusion could not be validated in our study because of the rare positivity of hepatitis B virus surface antigen in this patient population.

One noteworthy phenomenon was the potential hepatotoxicity of traditional Chinese medicine. The incidence of hepatotoxicity induced by traditional Chinese medicine was between 1.3 and 26.8% according to several available published studies and was usually the second or third most common reason for drug-induced liver injury [24,25]. In one patient in our study, liver function recovered to normal from grade III hepatotoxicity after discontinuation of a traditional Chinese medicine for 1 week. Our study reflected a relative actual situation for patients with long-term gefitinib administration, for that a large portion of elderly patients may need concurrent medications for their chronic comorbids, and that many Chinese patients tend to use traditional Chinese medicine during antitumor treatment. Thus, the results of our study have practical implications that be useful for physicians in their daily work.

Treatment of gefitinib-induced hepatotoxicity should be decided according to the grade of liver injury. In this study, most patients (35/36, 97%) with mild hepatotoxicity (grade I or II) still followed the gefitinib regimen. Under resolutions such as hepatoprotective medicine, reducing concurrent medication and intensive monitoring, all of these patients resumed normal liver function or grade I level of hepatotoxicity. However, the majority of patients (3/4, 75%) with severe hepatotoxicity (grade III) had discontinued their gefitinib regimen until resuming their liver function of lower than grade I hepatotoxicity after hepatoprotective medication. Several case reports suggest [26–29] that under conditions of severe hepatic dysfunction that cannot be treated with routine hepatoprotective treatment, switching to another *EGFR*-tyrosine kinase inhibitor such as erlotinib or dose reduction of gefitinib may be two possible choices.

In conclusion, our study showed that long-term gefitinib-induced hepatotoxicity was a common toxicity, with the majority of cases presenting elevated aminotransferase. Thus, regular monitoring of liver function and reduction of concurrent medication, especially those with potential liver toxicity (such as traditional Chinese medicines), are important during administration of gefitinib. Most patients with hepatotoxicity gained normal liver function and discontinuation of gefitinib was not necessary.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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