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ORIGINAL RESEARCH

Gefitinib frequently induces liver damage in patients with lung adenocarcinoma previously treated by chemotherapy

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Background: Gefitinib is known as one of the agents for treating patients with both advanced lung cancer and an epidermal growth-factor receptor mutation. In the epidermal growth-factor receptor-mutant advanced non-small-cell lung cancer population, gefitinib therapy has been associated with increased response rate, longer progression-free survival, and better quality of life compared to other anticancer drugs. However, gefitinib has to be discontinued for patients in whom adverse events occur, even if it is still effective. Here, we retrospectively assessed the clinical course of patients receiving gefitinib therapy, with a particular focus on liver damage.

Patients and methods: Of 24 Asian patients treated with 250 mg gefitinib daily at Kanagawa National Hospital, Japan, between January 2008 and June 2012, grade 3 liver damage (Common Terminology Criteria for Adverse Events, version 4.0) occurred in nine and were eligible for our assessment. The regimen was subsequently changed to alternate-day administration. The relationships between liver damage and each clinical factor were retrospectively examined using Fisher's exact test.

Results: Of the nine patients with liver damage, seven had previous exposure to another anticancer drug. There was a significant relationship between the incidence of liver damage and previous chemotherapy ($P = 0.009$). The objective response rates of patients treated with daily gefitinib 250 mg and alternate-day gefitinib following liver damage were 66.7% and 46.7%, respectively; these were not significantly different ($P = 0.597$).

Conclusion: Gefitinib for advanced adenocarcinoma patients who have previously undergone chemotherapy should be used cautiously and liver function monitored closely, because it frequently induces significant liver damage. The alternate-day administration of gefitinib may be a suitable option for patients in whom daily gefitinib therapy induces liver damage.

Keywords: gefitinib, liver damage, adjuvant chemotherapy, previous chemotherapy, alternate-day administration

Introduction

Gefitinib is a valuable therapeutic agent for patients with both advanced lung cancer and an epidermal growth-factor receptor (EGFR) mutation. As per the guidelines of the American Society of Clinical Oncology and the Japan Lung Cancer Society, it is recommended as a first-line treatment for patients with advanced non-small-cell lung cancer (NSCLC) and an EGFR mutation.[1] However, gefitinib therapy often needs to be discontinued due to the occurrence of adverse events, even if it remains clinically effective. In this retrospective study, we assessed the clinical course of patients receiving gefitinib therapy, with a particular focus on the extent of liver damage induced by the drug.

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Patients and methods

Patients

The present study was a retrospective analysis of all patients with pathologically proven adenocarcinoma who were treated at Kanagawa National Hospital, Japan, between January 2008 and June 2012. A total of 24 Asian patients (16 women, eight men, age 55–89 years, median 67 years) received gefitinib 250 mg/day; of these, ten patients had postoperative recurrence, while 14 patients had advanced inoperable cancer (Table 1). On admission, written informed consent was obtained from all patients in accordance with institutional guidelines based on the Helsinki Declaration. The relevant institutional review board approved this study.

Methods

Follow up assessments included physical examination, complete blood counts, blood chemistry evaluated every 2–4 weeks, and tumor assessment by computed tomography performed every 1–2 months.

Hepatitis B virus (HBV) surface antigen was detected by enzyme immunoassays as a serological marker of HBV infection, and anti-hepatitis C virus (HCV) antibody screening was performed using a chemiluminescent enzyme immunoassay (Ortho-clinical Diagnostics, Tokyo, Japan) before biopsy and/or surgical procedures in our hospital.

The tumor response was assessed as complete response (CR), partial response (PR), stable disease for ≥12 weeks (SD), or progressive disease (PD), in accordance with the standard guidelines for Response Evaluation Criteria In Solid Tumors.[2] Adverse events were evaluated using Common Terminology Criteria For Adverse Events version 4.0[3] (CTCAE). Liver damage was defined as elevation of serum levels of either liver or biliary enzymes. If a grade 3 adverse event occurred, daily administration of gefitinib was ceased and switched to alternate-day administration (250 mg/dose) after the serum levels of liver and biliary enzymes returned to the normal range.

For comparisons of proportions, Fisher's exact test was used. All results were considered significant at $P < 0.05$. All statistical analyses were performed using Stat Mate IV software version 4.01 (ATM, Tokyo, Japan).

Results

Patient characteristics are detailed in Table 1.

Table 1 Clinical characteristics of patients

	Previous chemotherapy		Total
	+	−	
Sex			
Female	7	9	16
Male	3	5	8
Age in years (median)	56–89 (64)	55–83 (67)	55–89 (67)
Smoking status			
Never smoked	6	8	14
Current smoker	2	2	4
Former smoker	2	1	3
Unknown	0	3	3
Hepatitis virus			
Hepatitis B virus antigen-positive	0	0	0
Hepatitis C virus antibody-positive	1	0	1
Alcohol consumption			
Nondrinker	8	7	15
Social drinker	1	3	4
0–20 g/day[a]	0	0	0
20–40 g/day[a]	1	1	2
≥40 g/day[a]	0	0	0
Unknown	0	3	3
Histology			
Adenocarcinoma	10	14	24
EGFR mutation			
Exon 18 G719X	1	0	1
Exon 19 deletion	1	7	8
Exon 21 L858R	4	3	7
None	2	1	3
Unknown	2	3	5
Operative and inoperative cases			
Postoperative recurrent or metastatic cases	4	6	10
Inoperable advanced cases	6	8	14
Performance status			
0	8	7	15
1	2	4	6
2	0	1	1
3	0	2	2
4	0	0	0
Metastasis or recurrence site[b]			
Bone	3	5	8
Pleurisy	2	4	6
Lung	3	3	6
Lymph node	3	3	6
Brain	0	3	6
Adrenal gland	2	0	2
Liver	1	0	1
Only tumor marker elevation	2	0	2

Notes: [a]Alcohol consumption was converted into pure alcohol; [b]some overlap present.
Abbreviation: EGFR, epidermal growth-factor receptor.

Hepatitis virus infection, smoking history, and alcohol consumption

Only one patient tested positive for HCV antibodies; the remaining patients showed negative results for HBV antigen and HCV antibodies. With regard to smoking status, the number of current smokers was four, there were three former smokers, and 14 patients had never smoked. The smoking status of the remaining three patients was unknown. With respect to alcohol consumption, the number of nondrinkers was 15, social drinkers four, and habitual drinkers (consuming pure alcohol $\geq$ 30.8 g/day) two.

EGFR mutation status

The following EGFR mutations were observed: exon 18 G719X (n = 1), exon 19 deletion (n = 8), and exon 21 L858R (n = 7). Three patients had no EGFR mutations, while the EGFR mutation status of five was not examined. The Eastern Cooperative Oncology Group Performance Status[4] was graded 0–1 in 21 cases and 2–3 in three patients. Of the 24 patients, ten patients had previously undergone chemotherapy, while 14 were chemotherapy-naive. All patients were initially treated with 250 mg gefitinib daily. CTCAE grade 3 liver damage occurred in nine of these patients; thereafter, the same dose was administered on alternate days.

Previous chemotherapy

Previous chemotherapy regimens as first-line therapy included the following: cisplatin (CDDP) 80 mg/m^2 plus docetaxel (DOC) 60 mg/m^2 (n = 2), CDDP 75 mg/m^2 plus pemetrexed sodium (PEM) 500 mg/m^2 (n = 2), carboplatin (CBDCA) (area under the curve = 5 mg/mL/minute) plus PEM 500 mg/m^2 (n = 1), CBDCA area under the curve = 5 mg/mL plus DOC 60 mg/m^2 (n = 1), CDDP 75 mg/m^2 plus PEM 500 mg/m^2 and bevacizumab 15 mg/kg (n = 1), gemcitabine (GEM) 1000 mg/m^2 and vinorelbine (VNR) 25mg/m^2 (n = 1), and tegafur-uracil 250 mg/m^2 a day for 2 years (n = 2).[5–10] Previous chemotherapy regimens as second-line therapy included the following: GEM plus VNR (n = 1), PEM 500 mg/m^2 (n = 1), and DOC 60 mg/m^2 (n = 1).[11,12] In four postoperative patients who underwent adjuvant therapy, two patients received tegafur–uracil, one patient was treated with CBDCA and PEM, and one patient was administered CDDP and PEM (Table 2).

Adverse events

Nine patients suffered CTCAE grade 3 liver damage, which occurred within 35–386 days (median 105 days) after the initiation of gefitinib therapy. The interval between cessation of gefitinib therapy and the normalization of the serum levels of both liver and biliary enzymes ranged from 7 to 22 days (median 13) (Table 3). Of the nine patients with liver damage, seven had previously been treated with other anticancer agents. The incidence of gefitinib-induced liver damage was significantly related to previous chemotherapy (P = 0.009, Tables 4 and 5).

Furthermore, skin rash occurred in ten patients (41.7%), liver damage in nine (37.5%), diarrhea in four (16.7%), and acute lung injury in two (8.3%) following gefitinib therapy.

Objective response rate

Overall, two patients achieved CR and eleven patients achieved PR. SD and PD were achieved in four and seven patients, respectively, as the best response. The objective

Table 2 Chemotherapy regimens before gefitinib treatment, alcohol history, and hepatitis virus

Liver damage induced by gefitinib	1st regimen before gefitinib therapy	2nd regimen before gefitinib therapy	Alcohol consumption	Hepatitis virus
Occurred	CDDP + DOC[a]	–	Nondrinker	Negative
	CDDP + PEM[b]	DOC[a]	Nondrinker	Negative
	CDDP + PEM[a]	GEM + VNR[a]	30.8 g/day	Negative
	CBDCA + PEM[a]	–	Nondrinker	Negative
	CBDCA + DOC[b]	–	Nondrinker	HCV
	UFT[b]	–	Nondrinker	Negative
	UFT[b]	–	Nondrinker	Negative
Did not occur	CDDP + DOC[a]	PEM[a]	Social drinker	Negative
	CDDP + PEM + BEV[a]	–	Nondrinker	Negative
	GEM + VNR[a]	–	Nondrinker	Negative

Notes: [a]Chemotherapy for postoperative recurrence or inoperative cases; [b]postoperative adjuvant chemotherapy.
Abbreviations: CDDP, cisplatin; DOC, docetaxel; PEM, pemetrexed sodium; GEM, gemcitabine; VNR, vinorelbine; CBDCA, carboplatin; UFT, tegafur-uracil; BEV, bevacizumab; HCV, hepatitis C virus.

Table 3 Patient characteristics of subjects receiving alternate-day gefitinib therapy following liver damage

Age (years)	Sex	Alcohol consumption	Hepatitis virus	Previous chemotherapy	Type of EGFR mutation	Days from initiating gefitinib treatment to cessation	Cessation (days)	Response rate
64	F	Nondrinker	None	–	Exon 19 deletion	35	13	CR
64	F	Nondrinker	None	+	Exon 21 L858R	36	7	PR
81	F	Nondrinker	Unknown	–	Exon 19 deletion	39	14	PD
88	M	Nondrinker	None	+	Exon 21 L858R	92	19	SD
62	F	Nondrinker	None	+	Exon 21 L858R	105	10	SD
62	F	30.8 g/day	None	+	Unknown	118	14	PR
80	M	Nondrinker	None	+	Exon 21 L858R	341	22	PR
70	F	Nondrinker	HCV	+	Exon 18 G719X	355	10	PR
60	F	Nondrinker	None	+	Exon 19 deletion	386	7	PR

Abbreviations: EGFR, epidermal growth-factor receptor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; HCV, hepatitis C virus.

response rates (ORRs) in all patients, patients with liver damage, and patients without liver damage were 54.2%, 66.7%, and 46.7%, respectively (Table 6). ORRs for patients treated with daily gefitinib (250 mg/day) and alternate-day gefitinib did not differ significantly ($P = 0.597$).

Discussion

The Iressa Pan-Asia Study demonstrated the noninferiority of gefitinib compared with CBDCA plus paclitaxel chemotherapy in terms of progression-free survival.[13] In some clinical studies of patients with EGFR mutations, gefitinib as first-line therapy led to a higher ORR and greater improvements in quality of life compared with CBDCA plus paclitaxel.[14–18] These reports supported that EGFR-mutant patients with advanced lung adenocarcinoma should receive an EGFR tyrosine kinase inhibitor (TKI) as first-line therapy.[15,19,20]

Some patients with completely resected NSCLC receive postoperative adjuvant chemotherapy that does not include EGFR TKI, but rather comprises CDDP-based anticancer drugs, despite the presence of EGFR mutations.[21] When recurrence or metastasis is clarified, EGFR-mutant

patients as well as patients with advanced NSCLC with EGFR mutations should receive an EGFR TKI as first-line therapy. Thus, we typically encounter patients with advanced NSCLC who have undergone previous chemotherapy as well as chemotherapy-naive patients in clinical practice.

In patients with gefitinib-induced liver damage, low-dose gefitinib treatment is efficacious; however, the clinical course and factors related to gefitinib-induced liver damage remain unknown.[22,23] Therefore, in the present study, we assessed the clinical factors related to gefitinib-induced liver damage in patients with inoperable advanced cancer or postoperative recurrence at a single general hospital.

Previous chemotherapy was significantly related to gefitinib-induced liver damage ($P = 0.009$, odds ratio = 14.0). No significant relationship was observed between gefitinib-induced liver damage and sex, performance status, postoperative recurrence or inoperable cancer, presence of skin rash and diarrhea, and the type of EGFR mutation (Tables 2 and 3). Among the ten postoperative recurrence patients who underwent postoperative adjuvant chemotherapy, liver damage occurred in four patients (40%). Therefore, it is important to monitor carefully the serum levels of liver and biliary enzymes during gefitinib treatment for patients who have previously received chemotherapy.

Table 4 Relationship between liver damage and each clinical factor

		Liver damage		P-value
		+	–	
Sex	Female/male	7/2	9/6	0.324
PS	0, 1/2, 3	8/1	13/2	0.692
Operation	+/–	4/5	6/9	0.739
Skin rash	+/–	5/4	5/10	0.260
Diarrhea	+/–	2/7	2/13	0.870
Previous chemotherapy	+/–	7/2	3/12	0.009*

Notes: Liver damage was significantly correlated with previous chemotherapy according to Fisher's exact test. *$P < 0.05$.
Abbreviation: PS, performance status.

Table 5 Relationship between previous chemotherapy and each adverse event

	Previous chemotherapy		P-value	Odds ratio
	+	–		
Liver damage	7	2	0.009*	14
Skin rash	4	6	0.780	0.89
Diarrhea	2	2	0.853	1.5
Acute lung injury	1	1	0.802	1.4

Note: Previous chemotherapy was significantly correlated with gefitinib-induced liver damage (odds ratio = 14). *$P < 0.05$.

Table 6 Objective response rate in patients administered daily gefitinib and alternate-day gefitinib following liver damage

	Gefitinib 250 mg/day	Reduced dose	Total
RECIST			
CR	1	1	2
PR	6	5	11
SD	2	2	4
PD	6	1	7
CR + PR (%)	7 (46.7)	6 (66.7)	13 (54.2)

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Liver damage is more frequently associated with gefitinib than with other chemotherapeutic regimens. Elevation of liver transaminases in grade 3 liver damage occurs at a frequency of 9% and 1% in patients treated with gefitinib and CBDCA plus paclitaxel, respectively.[13] In this study, only one HCV antibody-positive patient was included, while the other patients tested negative for HBV antigen and HCV antibodies; further, alcohol consumption was not excessive in the patient group, as shown in Table 1. Thus, we consider that the reason for the elevations in the serum levels of liver and biliary enzymes was neither hepatitis virus infection nor alcohol consumption. Furthermore, the relevance between liver damage and gefitinib was evaluated using the Digestive Disease Week Japan score,[24,25] which was modified for Japanese subjects based on the diagnostic criteria of the International Consensus Meeting.[26,27] The average of the Digestive Disease Week Japan score in our patients was 6.5 (cutoff score = 5).[24,25] Therefore, we considered that the liver damage observed in the nine patients in our study was caused by gefitinib.

The serum levels of liver and biliary enzymes returned to the normal range within approximately 2 weeks after the cessation of gefitinib therapy (Table 3). However, the recovery period included a bias related to the frequency of assessing these levels. After normalization of these enzyme levels, the alternate-day administration was performed safely. In terms of ORR, no significant differences were observed between patients treated with daily gefitinib and alternate-day gefitinib following liver damage. These results may suggest that treatment with gefitinib on alternate days be continued in such patients, even if liver damage occurs, given the clinical response to gefitinib.

The reason underlying the strong association between gefitinib-induced liver damage and previous exposure to other anticancer drugs remains unknown.[28] Because the nine patients with liver damage in our study had undergone chemotherapy using other anticancer drugs (eg, CDDP) without any adverse events beyond grade 3, it is unclear whether these anticancer drugs affected the liver enzyme levels. Gefitinib is metabolized by CYP3A4 and is O-demethylated by CYP2D6 in the liver.[29] Any anticancer drugs should be reduced or stopped generally in the setting of overt biochemical liver dysfunction, and Miller et al recommended a 50% dose reduction in erlotinib, another EGFR TKI, for lung adenocarcinoma patients with erlotinib-induced liver damage.[30,31] A liver biopsy would be necessary to assess accurately the mechanism underlying the liver damage induced by gefitinib in patients who have previously undergone chemotherapy.

Finally, based on the present findings, we recommend that the serum levels of liver and biliary enzymes be closely monitored during gefitinib treatment for patients who have received previous chemotherapy. This information may significantly contribute to improved clinical practice in terms of safety for anticancer drug administration to advanced lung cancer patients. Moreover, because alternate-day gefitinib treatment could be safely administered in patients in whom daily gefitinib therapy induced liver damage, we consider that this approach may be a suitable option in such patients in whom gefitinib continues to be clinically efficacious.

Our study has certain limitations. Further studies are necessary to confirm our findings, since the patient group in this study was not purely homogeneous, included patients with inoperable advanced cancer as well as those with postoperative recurrence, and had a small sample size because only a single general hospital was screened.

Conclusion

American Society of Clinical Oncology guidelines indicate that EGFR TKI therapy should be considered as a first-line therapy for patients with both advanced NSCLC and an EGFR mutation.[1,32–34] With regard to the incidence of adverse events, gefitinib should be cautiously used with monitoring liver function closely for advanced NSCLC patients who have previously undergone chemotherapy, because it frequently induces significant liver damage in such patients. Alternate-day administration of gefitinib may be a suitable option for patients in whom daily gefitinib therapy induces liver damage.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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