Acute Myocardial Infarction with Lung Cancer during Treatment with Gefitinib: the Possibility of Gefitinib-Induced Thrombosis

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Introduction

The Iressa (gefitinib) Dose Evaluation in Advanced Lung Cancer (IDEAL) 2 clinical trial indicated a good response rate in Japanese patients [1]. However, Cappuzzo et al. [2] reported that efficacy, toxicity, and symptom outcome in patients with non-small-cell lung cancer (NSCLC) treated with gefitinib do not seem to be related to epidermal growth factor receptor (EGFR) or HER2 expression. Recently, Lynch et al. [3] reported that a subgroup of patients with NSCLC had specific mutations in the EGFR gene, which correlated with clinical responsiveness to gefitinib. However, these findings may not explain the mechanism of gefitinib in many stable cases. The main anticancer mechanism of gefitinib in clinical cases remains unclear. On the other hand, severe adverse effects, including acute lung injury, interstitial pneumonia and alveolar hemorrhage, have been reported in Japan in patients receiving gefitinib [4, 5]. We describe a case of acute myocardial infarction with lung cancer experienced during treatment with gefitinib, since this may be one of the adverse effects induced by gefitinib.

Case Report

A 75-year-old female suffering from lung adenocarcinoma underwent right lower lobectomy 4 years previously. One year after the operation, she developed hypertension and diabetes mellitus. She did not suffer from hypercholesterolemia and did not smoke. Further, she had a relapse of lung cancer 1 year previously. The

administration of gefitinib was then started. A good response was observed but with a grade 1–2 skin adverse toxicity (table 1, period A). Two months later she complained of severe fatigue, and electrocardiography (ECG) revealed ischemic changes (table 1, period B). She was diagnosed with acute myocardial infarction. Therefore, the administration of gefitinib was halted. On admission day, ECG revealed sinus rhythm with an ST elevation in leads V_{1–3} and a T wave inversion in leads V_{3–6} (fig. 1). However, there were neither changes in ECG findings nor abnormalities in laboratory tests over the next 24 h (table 1, period C). On the other hand, echocardiographic findings were consistent with a diagnosis of myocardial infarction in the left anterior descending area. After 2 weeks' observation, the administration of gefitinib was restarted under the continued treatment with aspirin (table 1, period D). Following about 2 weeks' administration of gefitinib, a minor response of the lung cancer was observed. An analysis of platelet aggregation, stimulated by ADP or collagen before and after 2 weeks of receiving gefitinib, was performed. Both ADP and collagen-induced aggregations were suppressed before the restart of gefitinib. However, both the aggregations exhibited a tendency towards enhancement after the restart of gefitinib.

Discussion

We reported here the case of myocardial infarction experienced by a 75-year-old woman during the course of treatment with gefitinib for NSCLC. Gefitinib acts on the EGF pathway and in conjunction with radiation and tumor vasculature localization, endothelial cell damage and thrombosis occur under experimental conditions, and only in the indicated combination [6]. At least to our knowledge, thrombosis or myocardial infarction has not

Fig. 1. ECG findings at onset of myocardial infarction. ECG revealed sinus rhythm with an ST elevation in leads V₁₋₃ and a T wave inversion in leads V₃₋₆.

Table 1. Hematological and biochemical laboratory values

	Period				Normal values
	A	B	C	D	
Hematological data					
White-cell count, μ l	8,200	7,000	7,900	5,200	3,000–8,000
Red-cell count, $\times 10^4/\mu$ l	402	491	453	418	370–510
Hemoglobin, g/dl	10.4	13.1	12.0	10.8	11.3–15.4
Platelet count, $\times 10^4/\mu$ l	16.9	14.9	17.3	34.6	14–34
Biochemical data					
Total protein, g/dl	7.4	7.7	6.9	6.5	6.5–8.0
Aspartate aminotransferase, U/l	19	43	26	21	12–31
Alanine aminotransferase, U/l	11	16	13	10	6–24
Lactic acid dehydrogenase, U/l	191	265	208	190	105–210
Alkaline phosphatase, U/l	298	390	327	279	107–323
Urea nitrogen, mg/dl	33	23	23	30	8–20
Creatinine, mg/dl	1.03	0.87	0.83	0.95	0.40–0.80
Creatinine kinase, U/l	36	NT	46	21	39–160
C-reactive protein, mg/dl	0.05	0.06	0.20	0.17	0.00–0.30
C troponin I, ng/ml	0.03	NT	0.13	NT	0.00–0.10
Fibrinogen, mg/dl	300	NT	382	NT	150–350
Fasting blood sugar, mg/dl	243	250	295	222	60–100
Hemoglobin A1c, %	6.6	7.2	7.3	NT	3.9–5.9

A = Before admission; B = at onset of myocardial infarction; C = after onset of myocardial infarction; D = after admission; NT = not tested.

been published as a consequence or side effect of gefitinib. Therefore, as part of pharmacovigilance, it is deemed important to report relevant findings on such incidences occurring during new therapies. The present patient suddenly complained of general fatigue under the administration of gefitinib and showed ST-T abnormalities on ECG. In the laboratory data, the elevation of creatinine kinase was not confirmed, although it was seen that lactic acid dehydrogenase was increased. Therefore, it is difficult to diagnose whether the present case is one of angina or infarction by these results only. However, the findings on the echocardiograph strongly supported myocardial infarction. The patient received aspirin to prevent relapse. In the platelet aggregation test, as aspirin seemed to work effectively, both ADP- and collagen-induced aggregations were suppressed. However, both the aggregations exhibited a tendency towards enhancement after the restart of gefitinib. These results of the aggregation test suggest that gefitinib may cause enhancement of the platelet function.

Recently, we reported that thromboxane (TX) B_2 increased and prostaglandin (PG) 6-keto $F_{2\alpha}/TXB_2$ ratio decreased in gefitinib-treated patients. However, these patients did not exhibit an increase of PGE_2 or PG6-keto

$F_{1\alpha}$ [7]. TXA_2 increases proliferation in the smooth muscle but PGI_2 decreased the vascular smooth muscle cell proliferation [8, 9]. Therefore, it was suggested that the vascular smooth muscle cell proliferation was induced in patients receiving gefitinib [7, 10]. We also reported that accelerated platelet aggregation was observed in patients receiving gefitinib. These findings may be related with the two contrary effects of gefitinib [7, 10]. The present case suggested the accentuation of platelet aggregability caused by gefitinib and also the possibility of inducing an episode of acute myocardial infarction due to the enhanced platelet aggregability.

Because of advanced age or smoking habits, patients with NSCLC may have some atherosclerotic risk factors. Moreover, platelet thrombosis tends to be more frequent than fibrin thrombosis in Japan. Gefitinib may accelerate thromboembolic diseases by TX/PG imbalance and platelet activation. We preliminarily employed aspirin in order to prevent thrombosis in some patients receiving gefitinib treatment. So far, we have not seen any case of thrombosis. We suggest that careful observation should be exercised in patients with a history of thromboembolic diseases and atherosclerotic risk factors when administering gefitinib.

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