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CASE REPORT

Administration of gefitinib via nasogastric tube effectively improved the performance status of a patient with lung adenocarcinoma-derived meningeal carcinomatosis

Takeshi Okuda · Hidetoshi Hayashi · Mitsugu Fujita · Hiromasa Yoshioka · Takayuki Tasaki · Kazuhiko Nakagawa · Amami Kato

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Abstract Meningeal carcinomatosis (MC) is a refractory disease with a dismal prognosis, and no therapeutic strategy has been established to date. Herein we report a case of lung adenocarcinoma-derived MC in which the patient's performance status was dramatically improved by administration of gefitinib suspension via a nasogastric tube. The patient was a 71-year-old woman who was originally admitted to our hospital for a progressive headache and subsequently presented with severe consciousness disturbance. Cerebrospinal fluid examination and systemic imaging studies revealed MC that was derived from lung adenocarcinoma. Moreover, epidermal growth factor receptor (*EGFR*) mutations were detected in the tumor cells. Since the patient suffered from hydrocephalus, a ventriculoperitoneal shunt was placed. Nevertheless, her consciousness disturbance persisted. Subsequently, gefitinib suspension was prepared and administered via nasogastric tube, which dramatically improved her consciousness level and enabled her to tolerate oral intake. She died 14 months after the disease onset. The observations in this case report suggest that gefitinib might be a therapeutic option for patients with MC derived from cancers harboring *EGFR* mutations even though the patient exhibited severe consciousness disturbance.

Keywords Meningeal carcinomatosis · Lung adenocarcinoma · Gefitinib

T. Okuda (✉) · H. Yoshioka · T. Tasaki · A. Kato
Department of Neurosurgery, Kinki University Faculty of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan
e-mail: okuda@med.kindai.ac.jp

H. Hayashi · K. Nakagawa
Department of Medical Oncology, Kinki University Faculty of Medicine, Osaka, Japan

M. Fujita
Department of Microbiology, Kinki University Faculty of Medicine, Osaka, Japan

Introduction

Meningeal carcinomatosis (MC) is a refractory disease with a dismal prognosis that occurs in 5–10 % of cancer patients [1]. No therapeutic strategy has been established to date; the median survival time is 4–6 weeks if the disease is left untreated [1]. On the other hand, the recent development of novel chemotherapies has markedly improved the outcome of advanced cancer patients. The advent of molecular-targeted drugs is the most prominent among them, and gefitinib is a representative drug for lung cancer. Gefitinib has been shown to prolong the progression-free survival of patients with lung cancer harboring epidermal growth factor receptor (*EGFR*) mutations compared with standard chemotherapy [2, 3]. However, gefitinib is supplied in a tablet form and therefore needs to be administered orally. For this reason, patients with brain metastasis and/or MC sometimes have difficulty tolerating standard gefitinib treatment because they frequently exhibit consciousness disturbance and/or swallowing difficulty. Herein we report a case of lung adenocarcinoma-derived MC in which the patient's performance status (PS) was dramatically improved by administration of gefitinib suspension via a nasogastric (NG) tube even though the patient exhibited severe consciousness disturbance.

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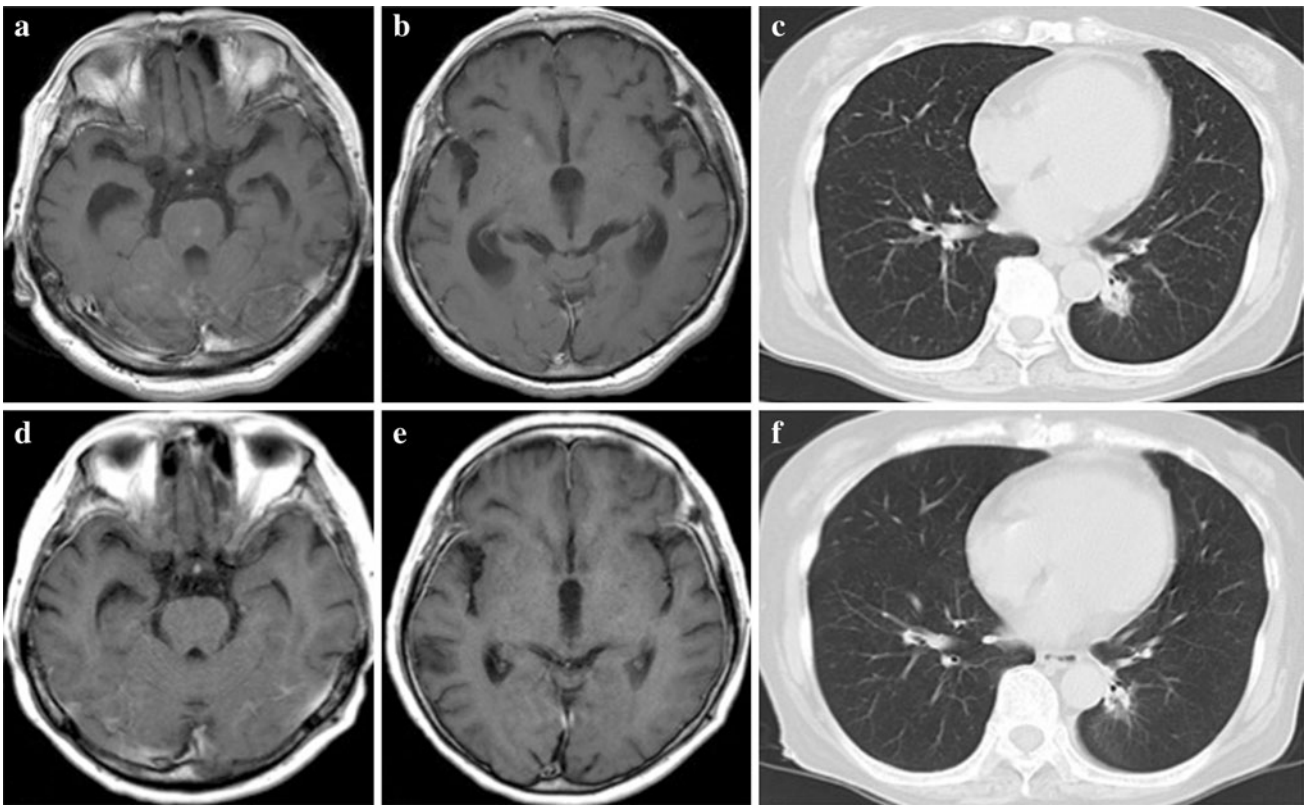

Fig. 1 Imaging studies pre- and post-gefitinib treatment. **a**, **b** T1-weighted gadolinium-enhanced MRI of the head reveals multiple small enhanced lesions. **c** Chest CT shows a mass-like lesion in the left lung S6 with diffuse granular shadows. **d**, **e** T1-weighted gadolinium-enhanced MRI reveals complete disappearance of the enhanced lesions. **f** Chest CT shows a decrease in size of the primary lesion

Case report

The patient was a 71-year-old woman who suffered from a progressive headache that had lasted several weeks. She suddenly presented with consciousness disturbance and was emergently admitted to our hospital. At the time of admission, her consciousness level was lethargic. Her past medical history was unremarkable. Magnetic resonance images (MRI) of the head revealed multiple small enhanced lesions and hydrocephalus (Fig. 1a, b). Cerebrospinal fluid (CSF) examination showed a cell count of 18/3 mm^3, protein 44 mg/dl, glucose 42 mg/dl, and carcinoembryonic antigen (CEA) 54.4 ng/ml (serum CEA 13.5 ng/ml). Adenocarcinoma cells were detected in the CSF. At the same time, computed tomography (CT) revealed a mass-like lesion in the left lung S6 segment along with diffuse granular shadows (Fig. 1c). These findings led us to diagnose MC that was derived from lung adenocarcinoma (cT1N0M1). *EGFR* mutations were also detected in exon 19 in the tumor cells, which was considered an appropriate target of gefitinib treatment.

Figure 2 shows the clinical course of the patient after the admission. The patient's consciousness level needed to recover for her to receive standard gefitinib treatment orally. Therefore we decided to place a ventriculoperitoneal (VP) shunt to treat the hydrocephalus. Nevertheless, the VP shunt failed to improve her consciousness level. Then, we sought to administer gefitinib suspension to the patient via an NG tube. Gefitinib tablets were finely crushed and suspended in 50 ml of sterile water (Fig. 3), and the patient received 250 mg/day gefitinib via an NG tube. On day 10 after the initiation of gefitinib treatment, her consciousness level improved dramatically, and she was able to tolerate oral intake on the following day. The imaging findings concurrently improved on the follow-up MRIs and CT (Fig. 1d–f). CSF cytology turned out to be negative on day 28. At the same time, CEA levels in the CSF also decreased to 11.3 ng/ml (serum CEA 11.8 ng/ml). The patient recovered with no neurological deficits and no adverse reactions. Gefitinib treatment was continued orally, and the patient was transferred for rehabilitation on day 82. She died 14 months after the disease onset without the cause of death identified.

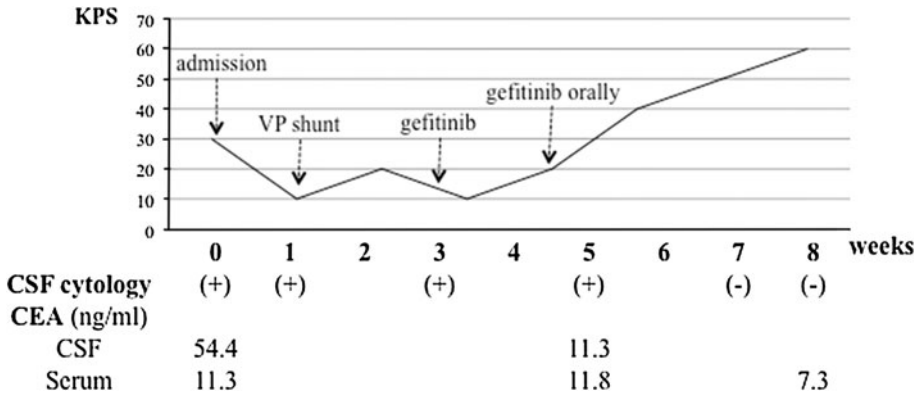

Fig. 2 Clinical course of the MC patient. *KPS* Karnofsky performance status, *CSF* cerebrospinal fluid, *CEA* carcinoembryonic antigen

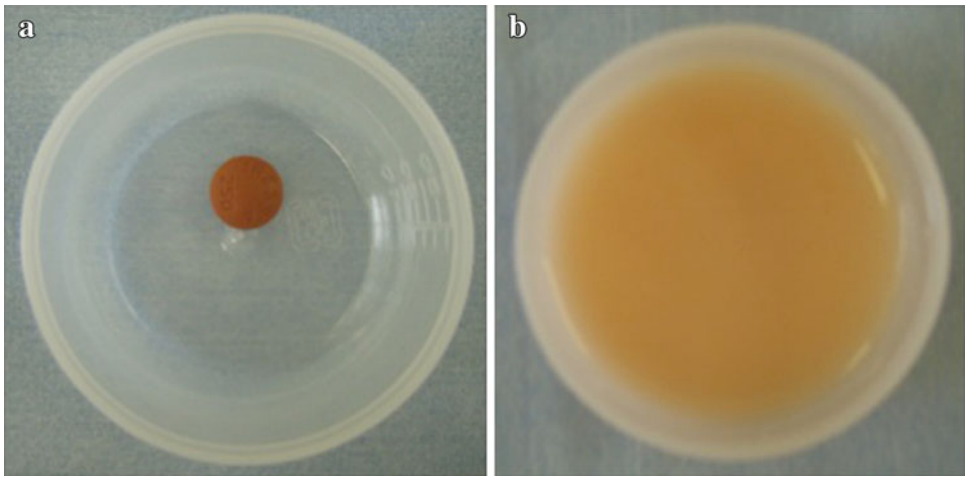

Fig. 3 Gefitinib processing for trans-NG tube administration. **a** Original gefitinib tablet. **b** Suspension of gefitinib in sterile water

Discussion

First-line gefitinib has been shown to improve the outcome of poor PS patients with *EGFR* mutation-positive lung cancers [4]. Therefore, examination of EGFR mutation as a biomarker is recommended in this patient population. However, since gefitinib is supplied in a tablet form and usually administered orally, standard gefitinib treatment is sometimes difficult for those with brain metastasis and/or MC because they frequently exhibit consciousness disturbance and/or swallowing difficulties. To treat these patients harboring *EGFR* mutations, gefitinib can be used in suspension by partially breaking the film coating and adding water [5]. Of note, the tablet film coating is not intended to enable sustained release or provide an enteric coating. Furthermore, administration of gefitinib suspension is comparable to administration of tablets in terms of bioavailability and safety [5]. On the basis of these findings, we postulated that the gefitinib suspension could provide the same therapeutic effect in this patient as the gefitinib tablets. Indeed, this therapeutic strategy successfully improved the patient's PS even though she had exhibited severe consciousness disturbance.

Although gefitinib is a small molecule inhibitor, intrathecal transfer rate is generally very low [6]. Particularly in MC patients, the concentration of gefitinib in the CSF has been reported as less than 1 % of the serum concentration [7, 8]. Nevertheless, the administration of gefitinib suspension improved the patient's PS in this case. We speculate several reasons for this. One is that even a low concentration of gefitinib would be effective against *EGFR* mutation-positive MC. Another reason is that the MC would destroy the blood–brain barrier (BBB) in situ and accelerate the drug transfer to each lesion. Indeed, whole-brain irradiation has been shown to enhance the intrathecal delivery of gefitinib by disruption of the BBB [9].

Erlotinib has been shown to induce higher bioactivities in plasma than gefitinib at similar or even lower doses of administration [10]. In addition, intrathecal gefitinib/erlotinib concentration can be elevated in a dose-escalating manner [7]. These findings suggest that erlotinib can be an alternative option for patients with MC or brain metastases if the primary cancer cells harbor *EGFR* gene mutations. We are currently in the process of determining the therapeutic efficacy of erlotinib for those with brain metastases harboring *EGFR* mutations.

A remaining issue is drug resistance exhibited by cancers. In the case of gefitinib/erlotinib, this typically occurs 8–12 months from the initiation of treatment. Over 50 % of resistance is caused by a mutation in the ATP binding pocket of the EGFR kinase domain involving substitution of a small polar threonine residue with a large nonpolar methionine residue (T790M) [11, 12]. In this regard, commencing treatment with a number of different therapeutic agents with differing modes of action is proposed to overcome the development of T790M and other resistance-conferring mutations [13].

In conclusion, we have reported the case of lung adenocarcinoma-derived MC in which the patient's PS was dramatically improved by the administration of gefitinib via an NG tube. The observations in this case report suggest that gefitinib/erlotinib might be therapeutic options for patients with MC derived from cancers harboring *EGFR* mutations even for the patients exhibiting severe consciousness disturbance.

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Conflict of interest The authors declare that we have no conflict of interest.

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