Long-term Outcome after Multidisciplinary Approach for Leptomeningeal Carcinomatosis in a Non-small Cell Lung Cancer Patient with Poor Performance Status

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Abstract

The present study describes a case of a 60-year-old Japanese man who was histologically diagnosed with lung adenocarcinoma harboring L858R mutation of epidermal growth factor receptor. He was successfully treated with gefitinib, but eventually developed leptomeningeal carcinomatosis. He underwent ventriculoperitoneal shunting for hydrocephalus and received erlotinib in place of gefitinib with concurrent whole brain radiotherapy; this resulted in dramatic improvement in his symptoms and performance status from four to one and he survived for as long as 13.6 months after the initiation of erlotinib therapy. This multidisciplinary approach may be particularly useful in terms of increasing survival and improving quality of life.

Key words: erlotinib, leptomeningeal carcinomatosis, gefitinib, non-small cell lung cancer, ventriculoperitoneal shunting

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Introduction

Leptomeningeal carcinomatosis occurs in approximately 5% of patients with cancer, and the median survival of patients with this disorder is 4 to 6 weeks without treatment. (1) Although symptomatic sites or areas of bulk disease evident on neuro-imaging studies are a possible target of radiation therapy, microscopic tumor on the leptomeningeal surface or tumor cells floating in the cerebral spinal fluid (CSF) usually limit treatment to intrathecal chemotherapy alone. Even in response to frequently used combination intrathecal chemotherapy with methotrexate, cytosine arabinoside and hydrocortisone (1, 2), median survival in these patients is limited to 18.6 weeks.

Recent reports suggest that epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) induce an early and dramatic response in patients with non-small cell lung cancer (NSCLC) (3). Subgroup analyses revealed that responsiveness to EGFR-TKI is more frequently observed in female nonsmokers with adenocarcinoma and is associated with specific gain of function mutations at exon 18, 19 and 21 of the EGFR gene, which are found in 10% of NSCLC cases in Europe and the USA and in 26% of NSCLC cases in East Asia (4). Nevertheless, the central nervous system is known to be a frequent site of disease recurrence in patients with NSCLC, and about 10% of patients eventually develop leptomeningeal carcinomatosis, even after an initial response to gefitinib (5). Furthermore, leptomeningeal carcinomatosis is associated with poor prognosis in patients with Eastern Cooperative Oncology Group performance status (ECOG PS) of 4 (6, 7). Therefore, an analysis of available data (mainly case reports) is warranted to determine what treatment modalities may be effective for this life-threatening...
complication of NSCLC.

The current study describes a case of a patient with gefitinib-refractory leptomeningeal carcinomatosis harboring L858R mutation of EGFR who was successfully treated with a multidisciplinary approach, including erlotinib, ventriculoperitoneal (VP) shunting, and concurrent whole brain radiotherapy (WBRT). Following the case presentation, we will discuss the treatment strategy for leptomeningeal carcinomatosis through a review of pertinent reports of leptomeningeal carcinomatosis in NSCLC patients with poor PS.

Case Report

A 60-year-old Japanese man was admitted to our hospital in January 2009 because of nausea and headache. Six years before admission, he was diagnosed with lung adenocarcinoma and underwent right upper lobectomy. The lung adenocarcinoma was pathologically characterized as T4N2M0, stage IIIB according to the TNM classification of the International Union Against Cancer (UICC) (8). Three years later, the tumor had relapsed at the surgical margin and had spread to the bilateral adrenal glands and sacrum. He received first-line chemotherapy with cisplatin (80 mg/m², day 1) and gemcitabine (1,000 mg/m², days 1 and 8), but therapy was discontinued after the first cycle due to the development of a grade two rash, as assessed by the Common Terminology Criteria for Adverse Events Version 3.0 grading system proposed by the National Cancer Institute. He subsequently received second-line treatment with docetaxel (60 mg/m², day 1). He received six cycles of this treatment and showed radiological partial response, according to the Response Evaluation Criteria in Solid Tumours (RECIST). In September 2007, he had recurrence in the sacrum and underwent radiation therapy (39 Gy/13 Fr). He also developed brain mass lesion and was diagnosed with intraparenchymal metastasis by surgical expiration. Sequencing analysis of the tumor sample revealed L858R mutation at exon 21 of EGFR, which is associated with sensitivity to EGFR-TKI therapy. Thus, gefitinib (250 mg/day) was initiated, resulting in clinical and radiological partial response on monthly follow-up evaluations. Two months before admission (15 months after starting gefitinib), he complained of headache, emesis, and sensory disturbance of the left upper extremity.

On admission, he developed impaired consciousness, and his ECOG PS worsened to 4. Gadolinium-enhanced magnetic resonance imaging (MRI) scans of the brain, which are more sensitive than computed tomography (CT) scanning for leptomeningeal carcinomatosis, did not show any identifiable mass lesion or leptomeningeal enhancement but did show hydrocephalus with ventricular enlargement (Fig. 1) (1). Laboratory testing showed decreased serum levels of total protein (6.4 g/dL), albumin (3.5 g/dL), and sodium (126 mEq/L). The serum carcinoembryonic antigen (CEA) level had increased to 15.0 ng/mL. He underwent VP shunting to relieve increased pressure inside the skull due to excess CSF and was diagnosed with leptomeningeal carcinomatosis after detection of adenocarcinoma cells in the CSF. Following this surgical procedure, gefitinib was stopped at 429 days after the initiation, and erlotinib (150 mg/day) was started with concurrent WBRT (30 Gy/10 Fr), not the craniospinal irradiation because his general condition did not seem to be tolerable to the complications caused by craniospinal irradiation. Clinical neurological improvement was noted within a week, and the tumor cells were no longer detected in the CSF. At the time of discharge, he had sufficiently recovered to be ambulatory and sustain work of a light or sedentary nature, sometimes accompanied by mild headache (PS of 1). Although he gradually developed cough, hemoptysis, and dyspnea on effort related to progression of pulmonary malignancy at 5 months after starting erlotinib therapy, he continued to receive erlotinib. He died as a result of his malignancy at 407 days after the start of erlotinib therapy.

Figure 1. Brain magnetic resonance imaging (MRI; T1 with gadolinium). Hydrocephalus associated with moderate enlargement of the third ventricular space without mass lesion or leptomeningeal enhancement was seen. (a), coronal section; (b), axial section.
Table 1. Clinical Characteristics of Patients with Lung Adenocarcinoma Harboring EGFR Mutation, Leptomeningeal Carcinoma, and PS of 4

<table>
<thead>
<tr>
<th>Patient</th>
<th>Author</th>
<th>Age / Gender</th>
<th>EGFR mutation</th>
<th>Initial EGFR-TKI</th>
<th>Response to initial EGFR-TKI</th>
<th>TTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Katayama et al.</td>
<td>81/M</td>
<td>X19del</td>
<td>Gefitinib</td>
<td>CR</td>
<td>275 days</td>
</tr>
<tr>
<td>2</td>
<td>Choong et al.</td>
<td>70/W</td>
<td>L858R+G884K</td>
<td>Erlotinib</td>
<td>SD</td>
<td>330 days</td>
</tr>
<tr>
<td>3</td>
<td>Katayama et al.</td>
<td>58/W</td>
<td>L858R</td>
<td>Gefitinib</td>
<td>SD</td>
<td>113 days</td>
</tr>
<tr>
<td>4</td>
<td>Katayama et al.</td>
<td>60/W</td>
<td>L858R</td>
<td>Gefitinib</td>
<td>NR</td>
<td>242 days</td>
</tr>
<tr>
<td>5</td>
<td>Nagano et al.</td>
<td>60/M</td>
<td>L858R</td>
<td>Gefitinib</td>
<td>PR</td>
<td>398 days</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; TTF, time to treatment failure; M, man; W, woman; X19del, exon 19 deletion; CR, complete response, disappearance of all target lesions; SD, stable disease, neither PR nor progressive disease (PD) criteria which means at least 20% increase in the sum of the LD of all target lesions, were met; NR, not reported.

Table 2. Summary of Responses to Treatments of Patients with Lung Adenocarcinoma Harboring EGFR Mutation, Leptomeningeal Carcinoma, and PS of 4

<table>
<thead>
<tr>
<th>Patient</th>
<th>VP shunting</th>
<th>WBRT</th>
<th>EGFR-TKI after leptomeningeal carcinomatosis</th>
<th>Clinical response of leptomeningeal carcinomatosis (ECOG PS)</th>
<th>Survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NR</td>
<td>NR</td>
<td>Erlotinib</td>
<td>Improved (4 → 4)</td>
<td>178 days</td>
</tr>
<tr>
<td>2</td>
<td>NR</td>
<td>NR</td>
<td>Gefitinib</td>
<td>Improved (4 → 2)</td>
<td>247 days</td>
</tr>
<tr>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>Erlotinib</td>
<td>Improved (4 → 3)</td>
<td>60 days</td>
</tr>
<tr>
<td>4</td>
<td>NR</td>
<td>NR</td>
<td>Erlotinib</td>
<td>Progress (4 → 4)</td>
<td>15 days</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>Erlotinib</td>
<td>Improved (4 → 1)</td>
<td>407 days</td>
</tr>
</tbody>
</table>

*:, the period between the start of EGFR-TKI after leptomeningeal carcinomatosis and death; VP, ventriculoperitoneal; WBRT, whole brain radiotherapy; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; PS, performance status; NR, not reported.

Discussion

Patient survival was longer in the present report than in previous reports describing similar patients. Regardless of the initial response to EGFR-TKI, the survival time following initiation of EGFR-TKI after leptomeningeal carcinomatosis remains less than 9 months in patients with PS of 4 who have NSCLC harboring an EGFR mutation (6, 7). The clinical characteristics and responses to treatments of patients with lung adenocarcinoma harboring EGFR mutation, leptomeningeal carcinoma, and PS of 4 described in the literature are summarized in Tables 1 and 2, respectively. It is noted that the mutational profiling of EGFR in leptomeningeal carcinomatosis can predict the response to EGFR-TKIs and that some EGFR mutations were reported to modulate differential responses to erlotinib and gefitinib, respectively, although they are similar anilinoquinazoline EGFR-TKIs (6). Katayama et al reported that some patients with gefitinib-refractory leptomeningeal carcinomatosis harboring an exon 19 deletion and exon 21 L858R mutations of EGFR were successfully treated with erlotinib (7). On the other hand, tumors with double mutation of L858R and E884K are more sensitive to gefitinib, because E884K, whose frequency is still not known among NSCLC patients, sensitizes the receptor to gefitinib and renders it more resistant to erlotinib (6).

The incomplete CSF penetration of gefitinib and the potential differences of dose equivalency between gefitinib and erlotinib may account for the favorable outcome in response to erlotinib of leptomeningeal carcinomatosis harboring exon 19 deletion and exon 21 L858R mutations of EGFR. As shown in several studies, the concentration of gefitinib in the central nervous system (CNS) is very low with standard dosing, and an increased dose of gefitinib is an effective therapeutic option for leptomeningeal carcinomatosis (9, 10). In a case described by Jackman et al, tumors of the lung, liver, and intestine had a T790M mutation, which conferred resistance to EGFR-TKI, but this mutation was not present in CNS tumor specimens (9). This report suggests that leptomeningeal carcinomatosis during gefitinib administration might have been caused, not by intrinsic resistance to gefitinib, but rather by incomplete drug penetration into the CNS. Although the approved daily dose of erlotinib (150 mg/day) is equal to the maximal tolerated dose (MTD), the standard dose of gefitinib (250 mg/day) is lower than the MTD, because response and survival were not different between 250 and 500 mg of gefitinib among two phase II trials (11, 12). Thus, dosing of erlotinib close to the MTD is considered to achieve more effective drug concentrations in...
the CSF when compared with gefitinib.

In the present case, the patient underwent VP shunting to drain the excess fluid into the abdominal cavity and to relieve the pressure in the brain. This was followed by erlotinib with concurrent WBRT. A retrospective study of 37 patients with leptomeningeal carcinomatosis who required VP shunting for the management of intracranial hypertension reported that improvement was seen in 27 (77%) patients and that there was no procedure-related mortality, although subdural hematoma developed in one and shunt malfunction occurred in three (13). On the other hand, radiation provides palliation of local symptoms and ensures that tumors located in regions that will not be reliably reached by chemotherapy (e.g., nerve root sleeves, Virchow-Robin spaces, and the interior of bulky lesions) will receive therapy (1). In fact, some patients with leptomeningeal carcinomatosis harboring EGFR mutation who were treated with EGFR-TKI with concomitant administration of intrathecal chemotherapy and WBRT showed relatively long-term survival. However, unlike the present case, those patients did not receive EGFR-TKI prior to diagnosis of leptomeningeal carcinomatosis (10). Thus, it is difficult to exclude the possibility that VP shunting and concurrent WBRT contributed to the relatively long survival seen in these cases.

In conclusion, the present case illustrates improved survival with the use of a multidisciplinary approach in a patient with lung adenocarcinoma, leptomeningeal carcinoma, and a PS of 4. This multidisciplinary approach incorporating EGFR-TKI therapy may be particularly useful in terms of increasing survival and improving the quality of life.

The authors state that they have no Conflict of Interest (COI).

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References