Gefitinib (‘Iressa’, ZD1839) May Restore Chemosensitivity in NSCLC Patients?

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Abstract. Gefitinib (‘Iressa’, ZD1839) has promising antitumor activity in non-small cell lung cancer (NSCLC). However, patients with advanced NSCLC have few treatment options available if they are refractory to gefitinib. We describe four cases of patients with advanced NSCLC who previously responded to gefitinib and obtained significant tumor regression through retreatment with other cytotoxic agents. Gefitinib might restore chemosensitivity to previously chemorefractory patients.

Gefitinib (‘Iressa’, ZD1839) is an orally active epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells. Two previous phase II studies of gefitinib demonstrated overall response rates of 11.8-18.4%, median survival of 6.5-7.6 months, and 1-year survival rates of 29-35% in chemorefractory patients with non-small cell lung cancer (NSCLC) (1, 2). The introduction of gefitinib to the treatment of advanced NSCLC had great clinical impact (3-5). However, even in patients with partial or complete response, the median duration of response to gefitinib was 7.0-13.0 months (6), and these patients have little chance of being cured. Here, we describe four interesting cases that showed objective response to retreatment with cytotoxic agents as second-, third-, or fourth-line chemotherapy after developing resistance to gefitinib.

Patients and Methods

Between November 2000 and December 2003, 73 patients were treated with 250 mg/day gefitinib in Okayama University Hospital and Okayama Rosai Hospital, Japan.

Results

Eighteen patients (25%) achieved a partial response to gefitinib treatment. Of these, eight had progressive disease during administration of gefitinib and five received subsequent cytotoxic chemotherapy. Response to chemotherapy was not evaluable in one patient because magnetic resonance imaging revealed multiple asymptomatic brain metastases at day 5 of the first cycle of chemotherapy, which was discontinued and followed by whole-brain irradiation. The duration of gefitinib treatment in the patients listed in Table I varied from 2 to 24 months. Three patients were treated with front-line platinum-based triplet chemotherapy, which achieved partial response in only one patient and stable disease in two. As shown in Figure 1 and Table I, all patients achieved tumor regression with a decrease in tumor markers through sequential chemotherapy with cytotoxic agents after becoming refractory to gefitinib treatment.

Discussion

Two previous randomized phase III trials have confirmed that docetaxel treatment is associated with significant survival benefit in patients with advanced NSCLC previously treated with cisplatin-based chemotherapy regimens (7,8). However, the overall response rates in these trials ranged from 0.5 to 10.8% at most. Accordingly, patients failing front-line chemotherapy had objective response rates of around 10% with second- or third-line chemotherapy.
Chemotherapy is effective for all refractory patients who responded to gefitinib in our clinical experience. In particular, the second patient obtained significant tumor regression with the same regimens of triplet or doublet chemotherapy as had previously been given. This suggests that cells resistant to cytotoxic agents might have their chemosensitivity restored during or after 8 months of gefitinib treatment.

Gefitinib might alter the biological characteristics of tumor cells and restore sensitivity to chemotherapy, as observed in the second patient. The cytotoxic agents received after gefitinib treatment might be non-cross-resistant to gefitinib and prior chemotherapy. Interestingly, three patients achieved objective tumor regression with vinorelbine. Vinorelbine might be useful as second-, third-, or fourth-line chemotherapy in patients responding to gefitinib treatment. Tumor cells refractory to cisplatin-based chemotherapy and gefitinib might remain sensitive to vinca alkaloids, as cisplatin-resistant cells show collateral sensitivity to vinca alkaloids ex vivo (9). Gefitinib combined

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**Table I. Clinical characteristics of four patients receiving cytotoxic chemotherapy after becoming refractory to gefitinib.**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>Prior chemotherapy</th>
<th>Response</th>
<th>Duration of gefitinib treatment</th>
<th>Subsequent chemotherapy</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43/Male</td>
<td>CDDP/TXT/GEM</td>
<td>SD</td>
<td>12 months</td>
<td>CBDCA/TXL</td>
<td>PR</td>
</tr>
<tr>
<td>2</td>
<td>48/Male</td>
<td>CDDP/MMC/VDS/CDDP/TXT/CPT-11/VNR/GEM</td>
<td>PD/PR</td>
<td>8 months/PR</td>
<td>CDDP/TXT/CPT-11/VNR/GEM</td>
<td>SD/SD</td>
</tr>
<tr>
<td>3</td>
<td>77/Female</td>
<td>GEM</td>
<td>SD</td>
<td>2 months</td>
<td>VNR</td>
<td>PR</td>
</tr>
<tr>
<td>4</td>
<td>72/Male</td>
<td>CDDP/TXT/GEM</td>
<td>SD</td>
<td>24 months</td>
<td>VNR</td>
<td>SD</td>
</tr>
</tbody>
</table>

Abbreviations: CBDCA, carboplatin; CDDP, cisplatin; CPT-11, irinotecan; GEM, gemcitabine; MMC, mitomicin; NC; TXL, paclitaxel; TXT, docetaxel; VDS, vindesine; VNR, vinorelbine; SD, stable disease; PR, partial response by the standard Response Evaluation Criteria In Solid Tumors guideline (J Natl Cancer Inst 92: 205-216, 2000).
with vinorelbine caused severe toxicities in both in vivo experiments (10) and clinical trials (Safety Information from AstraZeneca KK, Japan, January 2003), which suggests that gefitinib and vinorelbine might attack the same population of cells by different mechanisms.

Two recent randomized phase III trials of gefitinib in combination with cisplatin-based chemotherapy failed to demonstrate superiority over chemotherapy alone (11,12), thus, the optimal combination of gefitinib and cytotoxic agents has not yet been established. Our patients showed significant response to retreatment with cytotoxic chemotherapy after treatment with gefitinib. Gefitinib seems to be more effective when combined with chemotherapy sequentially rather than concurrently. According to the hypothesis advocated by Goldie et al. (13), since gefitinib is effective in chemotherapy-refractory cases, and vice versa, alternating treatment with gefitinib and cytotoxic agents including vinorelbine seems to be one of the fascinating strategies for advanced NSCLC. It is important to ascertain the optimal schedule and combination of gefitinib and conventional cytotoxic agents. Further investigations are warranted to confirm the efficacy of sequential combination treatment in preclinical experiments and clinical trials.

In conclusion, patients who firstly responded and became refractory to gefitinib should retry chemotherapy, even if they were refractory to chemotherapy prior to receiving gefitinib.

References


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549