Editorial

Chemotherapy for lung cancer: still alive!

I recently read a very interesting article entitled ‘Efficacy of chemotherapy after first-line gefitinib therapy in EGFR mutation positive advanced non-small-cell lung cancer—data from a randomized Phase III study comparing gefitinib with carboplatin plus paclitaxel (NEJ002)’ (1). The NEJ002 trial is the first report to demonstrate the superiority of gefitinib over the standard care of platinum doublet chemotherapy as a first-line treatment for advanced non-small-cell lung cancer (NSCLC) harboring activating epidermal growth factor receptor (EGFR) gene mutations. Gefitinib was more effective in improving progression-free survival (PFS) and quality of life, but surprisingly did not provide a greater overall survival (OS) benefit because of the crossover setting (2,3).

Based on the sub-analysis of the preceding paper, the authors conclude that first-line treatment with gefitinib would not affect chemotherapy, despite several study limitations, including small sample size and retrospective design. I agree with their interpretation; however, very disappointingly, the authors only showed similar response rates between the initial chemotherapy and after the initial gefitinib treatment, but did not describe response duration or the number of chemotherapy cycles. In addition, multiple types of chemotherapy were evaluated as a single group.

Although this manuscript has substantial limitations, it suggests that patients treated with gefitinib as a first-line treatment can undergo full-powered intact chemotherapy for progressive disease according to the response evaluation criteria in solid tumors (RECIST).

Additionally, treatment sequence [whether EGFR tyrosine kinase inhibitor (TKI) followed or preceded chemotherapy] had no impact on OS. This conclusion contrasts with the overall results of five randomized controlled trials (RCTs), which showed that initial TKI treatment provides a marked substantial advantage for PFS, but not OS (4,6–9). Median OS of cohorts initially treated with chemotherapy were better than those of the initial EGFR TKI cohorts in four of six trials; median OS was similar between cohorts in one of the remaining trials. Additionally, treatment sequence [whether EGFR TKI followed or preceded chemotherapy] had no impact on OS. This conclusion contrasts with the overall results of five RCTs, which showed that initial TKI treatment provides a marked substantial advantage for PFS, but not OS. Median OS of cohorts initially treated with chemotherapy were better than those of the initial EGFR TKI cohorts in four of six trials; median OS was similar between cohorts in one of the remaining trials.

Taken together, these results indicate that when EGFR TKIs are employed first, close attention should be given to the timing of chemotherapy initiation, at least in regard to the RECIST PD. Chemotherapy is essential to increase patient survival rates since the OS in patients with advanced NSCLC harboring EGFR gene mutations is currently ~4 years (10). As Dr Kris described in the ASCO Educational Booklet, ‘in 2014, nearly all persons with lung cancers will receive and benefit from intravenous chemotherapies at some point in their illness. This being the case, it is imperative to understand how to best use and tailor chemotherapies with targeted agents.’ While not stated directly, the paper appears to suggest that in clinical practice, patients with progressive disease might not have the opportunity to switch from gefitinib to chemotherapy because physicians, as well as patients, prefer to use EGFR TKIs due to their moderate adverse events, oral intake and use in an outpatient setting. This treatment strategy tended to show shorter OS than that observed with chemotherapy followed by TKIs (the WJTOG3405 trial showed 36% of patients did not receive platinum doublet chemotherapy) (4,5 in Table 1).

Table 1. Phase III clinical trials comparing EGFR TKIs with chemotherapy in the first-line setting

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEJ002 (2009)</td>
<td>Gefitinib versus carboplatin/paclitaxel</td>
<td>230</td>
<td>10.8 versus 5.4 (P = 0.001)</td>
<td>30.5 versus 23.6 (P = 0.31)</td>
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<tr>
<td>2011 (3)</td>
<td></td>
<td></td>
<td>10.8 versus 5.4 (P = 0.001)</td>
<td>27.7 versus 26.6 (P = 0.48)</td>
</tr>
<tr>
<td>WJTOG3405 (2009)</td>
<td>Gefitinib versus cisplatin/docetaxel</td>
<td>177</td>
<td>9.2 versus 6.3 (P = 0.0001)</td>
<td>30.9 versus NR HR 1.64</td>
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<tr>
<td>2014 (5)</td>
<td></td>
<td></td>
<td>34.8 versus 37.3 HR 1.25</td>
<td></td>
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<tr>
<td>OPTIMAL (6)</td>
<td>Erlotinib versus carboplatin/gemcitabine</td>
<td>165</td>
<td>13.1 versus 4.6 (P = 0.0001)</td>
<td>34.8 versus 37.3 HR 1.25</td>
</tr>
<tr>
<td>EURTAC (7)</td>
<td>Erlotinib versus platinum-based chemotherapy</td>
<td>174</td>
<td>9.7 versus 5.2 (P = 0.0001)</td>
<td>19.3 versus 19.5 (P = 0.87)</td>
</tr>
<tr>
<td>LUX-Lung 3 (8)</td>
<td>Afatinib versus cisplatin/pemetrexed</td>
<td>345</td>
<td>11.1 versus 6.9 (P = 0.0004)</td>
<td>28.2 versus 28.2 HR 0.88 (P = 0.385)</td>
</tr>
<tr>
<td>LUX-Lung 6 (9)</td>
<td>Afatinib versus cisplatin/gemcitabine</td>
<td>364 (2:1)</td>
<td>11.0 versus 5.6 (P = 0.0001)</td>
<td>23.1 versus 23.5 HR 0.93 (P = 0.614)</td>
</tr>
</tbody>
</table>

HR, hazard ratio; OS, overall survival; PFS, progression-free survival; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NEJ, North-East Japan; WJTOG, West Japan Thoracic Oncology Group; EURTAC, European Tarceva versus chemotherapy; OPTIMAL, open label, Phase III study comparing first-line Tarceva versus cisplatin plus gemcitabine in Chinese advanced/metastatic non-small-cell lung cancer patients with EGFR activating mutations.
Even now, there is a deep-rooted antipathy to chemotherapy despite the availability of drugs to control the nausea and vomiting induced by cisplatin and the fact that it may now be implemented in an outpatient setting (11,12). In addition, NSCLC harboring EGFR gene mutations are sensitive to chemotherapies. Response rates in mutation + versus − are as follows: docetaxel 46 versus 0% (V-15-32), 21 versus 10% (INTEREST), carboplatin/paclitaxel 47 versus 27% (IPASS), 30% versus none (NEJ002). In Japanese subset analysis of LUX-lung 3, afatinib followed by cisplatin plus pemetrexed produced 46.9-month of median OS. In patients where an effective TKI can be found for the gene driving the cancer, such as gefitinib for the activating EGFR gene mutation, TKIs are routinely effective for ∼1 year. Rather than continuing to treat clinical PD, TKIs are most appropriate in combination with sequencing and other treatments, such as chemotherapy, immunotherapy, radiotherapy and/or surgery. Now we should aim for a 5-year survival rate, and if possible, a long-term and complete remission. These factors should be considered when constructing a comprehensive treatment plan for patients with advanced NSCLC harboring driver oncogenes.

Conflict of interest statement
Katsuyuki Kiura received honoraria from Chugai Pharmaceutical Co., Ltd, F. Hoffmann-La Roche AG, Genentech Eli Lilly Japan AstraZeneca K.K. and Nippon Boehringer Ingelheim Co., Ltd.

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References
5. Yoshioka H, Mitsudomi T, Morita S, et al. Final overall survival results of WJTOG 3405, a randomized phase 3 trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer (NSCLC) harboring mutations of the epidermal growth factor receptor (EGFR). J Clin Oncol 2014;32(suppl; abstr 8117):55.

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