Dose erlotinib add beneficial effect on cytotoxic agent for patients with pretreated advanced non-small cell lung cancer?

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Combination of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) with platinum-containing standard chemotherapy failed to provide better outcomes in the first-line setting for advanced non-small cell lung cancer (NSCLC) in several phase III trials. The approved monotherapy of erlotinib, pemetrexed or docetaxel as the second-line regimen still remains unsatisfactory in anti-tumor effects for recurrent NSCLC. Combination of EGFR-TKI with cytotoxic drug seemed a promising strategy to improve therapeutic outcome for pretreated advanced NSCLC, because preclinical studies indicated schedule-dependent administration of EGFR-TKI with a specific cytotoxic drug had synergistic anti-tumor effects against NSCLC cells. Several clinical pharmacokinetic analyses in dose-finding phase I studies revealed that intermittent erlotinib with pemetrexed or docetaxel did not induce any potential antagonism between two drugs when erlotinib and its metabolites were almost completely swept away from plasma at the subsequent pemetrexed or docetaxel dosing. Recently, four phase II studies of combination of erlotinib with pemetrexed or docetaxel in the second-line setting for patients with NSCLC were reported. As a result, additional anti-tumor effects of erlotinib on cytotoxic drug still remain controversial. Three phase II studies showed favorable results and supported combination strategy of erlotinib, but our study failed to demonstrate the benefits from combination of intermittent erlotinib with tri-weekly pemetrexed. Herein, we review whether combination of erlotinib with cytotoxic drug is a promising therapeutic approach as the second-line treatment for advanced NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); Epidermal growth factor receptor - tyrosine kinase inhibitor (EGFR-TKI); Erlotinib; Gefitinib;Pemetrexed; Docetaxel; second-line chemotherapy; combination chemotherapy


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Introduction

Lung cancer is the most common cause of cancer-death all over the world [¹]. It is roughly divided into two histological subtypes; non-small cell lung cancer (NSCLC) and small cell lung cancer. The former accounts for about 85% of all lung cancer cases. In most patients with NSCLC, diseases have already advanced locally or systemically
before diagnosis. Currently, docetaxel [2] (Taxotere®); a taxan anti-microtubule agent, pemetrexed [3] (Alimta®); a multi-targeting antifolate cytotoxic agent, and erlotinib [4] (Tarceva®); an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), have been approved for second-line treatment, regardless of EGFR mutation status, monotherapy using any of these agents is effective only in approximately 10% of patients. To improve therapeutic outcome, one may be to combine different cytotoxic agents, and another option may be to combine EGFR-TKI and cytotoxic chemotherapy. To date, no combination of two drugs, neither two cytotoxic drugs nor a cytotoxic drug plus an EGFR-TKI, has demonstrated a survival prolongation as a second-line regimen. Consequently, many patients give up treatment.

Erlotinib was shown to provide a survival prolongation for pretreated NSCLC patients, regardless of histological types and EGFR mutation status [4]. However, in two phase III randomized trials in untreated NSCLC patients; concomitant use of erlotinib with two kinds of standard first-line platinum-containing regimens; cisplatin plus gemcitabine (TALENt) and carboplatin plus paclitaxel (TRIBUTE), failed to improve survival [5, 6]. Gefitinib (Iressa®), another EGFR-TKI, was also shown to have no additional effect on standard first-line chemotherapy (INTACT-1, 2) [7, 8]. The additional use of erlotinib to paclitaxel and carboplatin had no influence on the pharmacokinetic and systemic exposure of each drug [9]. Nevertheless, a retrospective analysis of TRIBUTE trial demonstrated that the treatment effects such as response rate (RR) and time-to-progression tended to be lower in combination arm of erlotinib with standard chemotherapy than those in placebo arm [10], suggesting an antagonistic interaction between erlotinib and standard chemotherapy.

There is no established evidence of combination regimen of erlotinib with pemetrexed or docetaxel in second-line treatment for NSCLC. Herein, we reviewed whether combination of erlotinib with cytotoxic drug is a promising therapeutic approach as the second-line treatment for advanced NSCLC.

Preclinical evidence supporting combination of erlotinib with cytotoxic drug in NSCLC

Contrast to the negative results in some clinical phase III studies, some preclinical in vitro or xenograft experiments have suggested that the combination effects of EGFR-TKI with cytotoxic drug is synergistic against NSCLC. This discrepancy between clinical and preclinical studies can be explained by selected partner drug and effective administration schedule of the two drugs.

In NSCLC cells with wild-type EGFR, the combination effects of gefitinib with pemetrexed and anti-microtubule agents (paclitaxel, docetaxel or vinorelbine) were synergistic, while the combination effect of gefitinib with gemcitabine was only additive [11, 12]. In contrast, combination of gefitinib with cisplatin was antagonistic in both EGFR-mutated and non-mutated NSCLC cell lines, likely because gefitinib interfered with cisplatin entry into the cancer cell. The antagonism between EGFR-TKI and platinum is a possible reason for the failure of clinical phase III randomized trials [13].

The schedule of gefitinib administration is also important for the emergence of effective interaction of the two drugs, but is still controversial. Solits et al. showed by xenograft mice model that two days of intermittent administration of high dose gefitinib before paclitaxel had significantly greater anti-tumor activity compared with either drug alone or the combination of continuous daily gefitinib and paclitaxel [14]. Cheng et al. showed by in vitro cell line model that the sequence of paclitaxel followed by gefitinib was superior to other sequences [15, 16].

Compared with gefitinib, erlotinib has fewer preclinical studies of combination therapy. In the in vitro study by Li et al., cytotoxicity was synergistically enhanced when human NSCLC cells were cultured in the medium containing both pemetrexed and erlotinib concurrently, or that containing pemetrexed followed by erlotinib sequentially. These phenomena were observed, irrespective of the mutation status of EGFR or K-Ras gene. On the other hand, when cancer cells were exposed to erlotinib followed by pemetrexed, antagonistic and slight additive effects were observed in erlotinib-sensitive and erlotinib-resistant cells, respectively [17]. In the in vitro study by Giovannetti
Table 1. Comparison of phase I studies of combination erlotinib with docetaxel or pemetrexed.

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Tumor</th>
<th>Experimental Treatment</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranson</td>
<td>20</td>
<td>NSCLC (including 6 SQ)</td>
<td>PEM 500-700 mg/m² every 3 weeks + ERL 100-150 mg/day, daily.</td>
<td>PEM 500 mg/m², day 1, every 3 weeks + ERL 150 mg/day, daily</td>
</tr>
<tr>
<td>Davies</td>
<td>42</td>
<td>Any solid tumor (including 16 NSCLC and 4 SQ)</td>
<td>Arm A; PEM 500 mg/m², every 3 weeks + ERL 800-1400 mg/day, days 2, 9, and 16.</td>
<td>Arm A; PEM 500 mg/m², day 1, every 3 weeks + ERL 1400 mg/day, days 2, 9, and 16.</td>
</tr>
<tr>
<td>Minami</td>
<td>12</td>
<td>Non-SQ NCLC</td>
<td>PEM 500 mg/m², every 3 weeks + ERL 100-150 mg, days 2–16.</td>
<td>PEM 500 mg/m², day 1, every 3 weeks + ERL 150 mg/day, day 2-16</td>
</tr>
<tr>
<td>Chiorean</td>
<td>25</td>
<td>Any solid tumor (including 4 NSCLC)</td>
<td>DTX 20-35mg/m2, days 1, 8, and 15 every 4 weeks for up to 6 cycles + ERL 150mg/day daily for a maximum of 12 cycles.</td>
<td>DTX 30mg/m², day 1,8 and 15, every 4 weeks + ERL 150 mg/day daily</td>
</tr>
<tr>
<td>Sangha</td>
<td>42</td>
<td>Any solid tumor (including 22 NSCLC)</td>
<td>Arm A; DTX 70–75 mg/m² every 3 weeks + ERL600–1000 mg/day on days 2, 9, and 16.</td>
<td>DTX 70mg/m², day 1, every 3 weeks + ERL 200 mg/day, day 2-16</td>
</tr>
</tbody>
</table>


et al., synergistic cytotoxicity was examined in various treatment schedules in combination of pemetrexed and erlotinib. The more favorable synergistic effect was observed when 24-hour concurrent administration of erlotinib with pemetrexed was followed by 48-hour erlotinib than 72-hour single use of either agent or 72-hour combination use of both agents [18]. Thus, erlotinib also has schedule-dependent synergistic anti-tumor effects with pemetrexed. This schedule dependency of erlotinib is not limited to combination with pemetrexed. Docetaxel followed by erlotinib treatment showed nearly additive effects and had no inhibitory effects on docetaxel-induced apoptosis, but erlotinib followed by docetaxel treatment showed remarkable antagonistic interactions and reduced apoptosis induction compared with docetaxel alone [19]. The mechanisms of the synergism and antagonism of erlotinib with pemetrexed may be explained by cell cycle, intracellular signal pathway (Fig.1), and thymidylate synthase (TS) expression and activity.

Pemetrexed and erlotinib arrest an S-phase and a G1-phase of cell cycle, respectively. When pemetrexed arrests S-phase in advance and erlotinib arrests the G1-phase thereafter, their arrest activities are enhanced. Conversely, in the case of reverse order, erlotinib reduces the activity of S-phase arrest induced by pemetrexed. Namely, when erlotinib is administered after pemetrexed, erlotinib promotes the cytotoxicity of pemetrexed, pemetrexed retains cancer cells in M-phase where erlotinib exerts the greatest cytotoxic power. Hence, this sequential combination of erlotinib followed by pemetrexed induces more powerful anti-tumor activity. In contrast, when erlotinib is administered before pemetrexed, erlotinib causes G1 arrest, resulting in reduction of S-phase entry crucial for the exertion of pemetrexed-mediated cytotoxicity and antagonistic interaction. Pemetrexed also activates the phosphatidylinositol 3-kinase (PI3K) /AKT pathway, which is mediated by EGFR and blocked by erlotinib [17, 18]. Moreover, erlotinib also reduces TS expression and activity, possibly via E2F-1 reduction, which may augment the activity of pemetrexed [18]. Thus, erlotinib and pemetrexed work synergistically against NSCLC cells, and their genetic characteristics of EGFR and K-ras are not involved in this interaction in vitro.

These preclinical studies proposed that combination of erlotinib with cytotoxic agent is practically expected to offer synergistic antitumor efficacy.
Table 2. Comparison of phase II studies of combination erlotinib with docetaxel or pemetrexed as second-line treatment.

<table>
<thead>
<tr>
<th>Presenter /Author</th>
<th>n</th>
<th>Treatment</th>
<th>PFS (M)</th>
<th>OS (M)</th>
<th>RR (%)</th>
<th>DCR (%)</th>
<th>EGFR mutation status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pawel [31]</td>
<td>83</td>
<td>Monotherapy</td>
<td>PEM 500mg/m², day1, every 3 weeks</td>
<td>2.9</td>
<td>7.8</td>
<td>10.8</td>
<td>51.8</td>
</tr>
<tr>
<td></td>
<td>76</td>
<td>Combination</td>
<td>PEM 500mg/m², day1, every 3 weeks + ERL 150mg/day,daily</td>
<td>3.2</td>
<td>11.8</td>
<td>17.1</td>
<td>55.3</td>
</tr>
<tr>
<td>Aerts [28]</td>
<td>115</td>
<td>Monotherapy</td>
<td>ERL150mg/day daily</td>
<td>All 4.9</td>
<td>All 5.5</td>
<td>7</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PQM 500mg/m², day1, every 3 weeks</td>
<td>SQ 4.9</td>
<td>SQ 6.2</td>
<td>2</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NSQ 4.9</td>
<td>NSQ 5.5</td>
<td>10</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>116*</td>
<td>Combination;</td>
<td>ERL (days 2-16) + DTX 75 mg/m² for SQ or PEM 500mg/m² for NSQ, every 3 weeks +4cycles</td>
<td>All 6.1</td>
<td>All 7.8</td>
<td>13</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>34 SQ</td>
<td></td>
<td>SQ 4.1</td>
<td>SQ 6.1</td>
<td>6</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>82 NSQ</td>
<td></td>
<td>NSQ 7.2</td>
<td>NSQ 9.1</td>
<td>16</td>
<td>59</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>p = 0.06 (for All)</td>
<td>p = 0.01 (for All)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee [29]</td>
<td>240</td>
<td>Combination</td>
<td>PEM 500mg/m², day1, every 3 weeks + ERL 150mg/day, days 2-14.</td>
<td>7.4</td>
<td>20.5</td>
<td>44.7</td>
<td>64.5</td>
</tr>
<tr>
<td></td>
<td>78</td>
<td></td>
<td>ERL Monotherapy</td>
<td>ERL 150mg/day, daily</td>
<td>3.8</td>
<td>22.8</td>
<td>29.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PEM Monotherapy</td>
<td>PEM 500mg/m², day1, every 3 weeks</td>
<td>4.4</td>
<td>17.7</td>
<td>10.0</td>
</tr>
<tr>
<td>Minami [30]</td>
<td>27</td>
<td>Combination Single Arm</td>
<td>PEM 500mg/m², day1, every 3 weeks + ERL 150mg/day, days 2-16</td>
<td>2.8</td>
<td>15.8</td>
<td>11.1</td>
<td>63.0</td>
</tr>
<tr>
<td></td>
<td>(All NSQ)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>One positive</td>
</tr>
<tr>
<td>Sangha [24]</td>
<td>39</td>
<td>Combination Single Arm</td>
<td>DTX 70mg/m², day1, every 3 weeks + ERL 200 mg/day, days 2-16</td>
<td>4.1</td>
<td>18.2</td>
<td>28.1</td>
<td>64.1</td>
</tr>
<tr>
<td></td>
<td>(6 SQ)</td>
<td></td>
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</tr>
</tbody>
</table>

SQ; squamous cell carcinoma, NSQ; non-squamous cell carcinoma, PEM; pemetrexed, ERL; erlotinib, DTX; docetaxel, PFS; progression-free-survival, OS; overall survival, M; month, RR; response rate, DCR; disease control rate, ND; not described, EGFR; epidermal growth factor receptor

* Fifteen percent of the patients in the second-line pemetrexed combination subgroup received pemetrexed platinum treatment as first-line treatment. In the docetaxel combination arm, docetaxel platinum as first-line treatment was given to one patient.

** P-value in the study by Lee et al.; vs PEM+ERL arm

*** Whether or not EGFR mutation status was examined in all patients was not described. EGFR mutations identified using Scorpion-amplification refractory mutation system of circulating tumor DNA in plasma.

Phase I and pharmacokinetic studies of combination of erlotinib with pemetrexed or docetaxel

There are five phase I studies of combination of erlotinib with a cytotoxic agent; three pemetrexed studies [20-22] and two docetaxel studies [23, 24] (Table 1). The final recommended doses and administration schedules varied among studies.

Four studies conducted pharmacokinetic analysis. Davies et al. demonstrated that erlotinib nearly disappeared from plasma at the next administration of tri-weekly pemetrexed by the withdrawal of erlotinib for 5 days. In this study, the measurement of the trough plasma concentrations of erlotinib and erlotinib metabolite, OSI-420, were performed on day 21, one day before the second pemetrexed administration. Those were beneath
measurable threshold when 150 mg of erlotinib was administered on days 2-16, but not negligible when 1000 mg of erlotinib was administered weekly [29]. Ranson et al. showed that pemetrexed and erlotinib had no drug-drug pharmacokinetic interactions when pemetrexed was administered tri-weekly in combination with continuous daily erlotinib from day 1. No change was observed in the mean plasma concentration–time profiles of pemetrexed between day 1 and day 22, the start of the second cycle, and of erlotinib between day 20 and day 22 [22]. This result was expected because these two drugs are eliminated in different pathways. After oral administration, CYP3A4 plays a main role in metabolism of erlotinib, while CYP1A2 and CYP1A1 participate partly. Erlotinib is finally excreted in the feces [25, 26]. In contrast, after intravenous administration, pemetrexed is hardly metabolized and excreted mainly in the urine [27]. Similar pharmacokinetic of erlotinib that was observed in combination with pemetrexed was shown in combination with docetaxel. Chiorean et al. also revealed no pharmacokinetic interaction was observed when docetaxel was administered weekly (days 1, 8, and 15, every 4 weeks) in combination with continuous daily erlotinib. The pharmacokinetic variables of these two drugs were similar on day 1 of the second cycle to those of the historical controls of each drug [23], Sangha et al. showed that, with erlotinib dosing schedule of days 2-16, nadir plasma concentrations of erlotinib and its metabolite were either undetectable or far below therapeutic levels one day before their second cycle of docetaxel (day 21) [24]. Thus, erlotinib had no pharmacokinetic interaction with pemetrexed or docetaxel. Especially, intermittent administration of erlotinib enables subtherapeutic plasma concentration levels of erlotinib at the subsequent pemetrexed or docetaxel dosing to prevent potential antagonism between two drugs. This regimen supports the concept of pharmacodynamic separation as shown by some preclinical studies. Deliberate withdrawal of erlotinib for 5 days before the next administration of a cytotoxic drug is expected to release the G1-phase arrest activity of erlotinib and make cancer cells enter into S-phase.

**Phase II studies of combination of erlotinib with pemetrexed or docetaxel**

There are four phase II studies of combination of erlotinib with a cytotoxic agent; three pemetrexed studies [28-31] and one docetaxel study [34] (Table 2).

In NVALT-10 study, addition of pemetrexed or docetaxel to erlotinib failed to improve progression free survival (PFS) compared to erlotinib alone, the primary endpoint, but overall survival (OS), one of the secondary endpoints, was significantly improved in the combination arm. This improvement appears restricted to the non-squamous NSCLC patients who received combination therapy of erlotinib with pemetrexed [28]. The study by Lee et al. demonstrated that PFS, the primary endpoint, was improved by combination of erlotinib with pemetrexed in never-smokers with advanced NSCLC, but no statistically significant difference was found in OS, the secondary endpoint, between pemetrexed plus erlotinib and either single agent. The benefit was observed across multiple clinical and biomarker subgroups [29]. In the single arm study by Sangha on combination of intermittent erlotinib with tri-weekly docetaxel, the RR (28.1%) met the expected value (20%). The RR (28.1%), disease control rate (DCR) (64.1%), median PFS (4.1 months) and median OS (18.2 months) were better than those of the historical controls of each agent. These three studies favorably supported combination strategy of erlotinib with pemetrexed or docetaxel. On the other hand, our study (OSAKA-LCSG 0902 trial) did not show the benefits from combination of intermittent erlotinib with tri-weekly pemetrexed. The RR, the primary endpoint, was only 11.1% and failed to exceed the expected rate (33.5%). Our study was the only one in which EGFR mutation status was examined in all patients. All except one patient had wild-type EGFR [30]. The RR (11.1%), DCR (63.0%), median PFS (2.8 months) and median OS (15.8 months) of our study were superior to those (3.3%, 63.3%, 2.1 months and 9.2 months, respectively) of Okayama Lung Cancer Study Group trial 0705, a Japanese phase II trial of second to fourth line chemotherapy of erlotinib in patients with EGFR wild-type advanced NSCLC [32]. However, our results were similar to those of the previous two subgroup analyses of pemetrexed monotherapy in patients with pretreated advanced non-squamous NSCLC and unknown EGFR mutation status. In a randomized phase III study, the RR, PFS and OS of second-line pemetrexed monotherapy were 11.5%, 3.1 months and 9.3 months in median, respectively [33]. In a Japanese randomized phase II study, the RR, DCR, PFS and OS of 500mg/m² dose of second-to-third line pemetrexed monotherapy were 23.5%, 62.4%, 3.1 months and 19.4 months in median, respectively [34]. Comparing our study with the previous studies of erlotinib or pemetrexed monotherapy, erlotinib is not active in EGFR mutation-negative population. In our study, we thought that only pemetrexed exhibited the majority of anti-tumor effects. Therefore, we are skeptical to the add-on effects of erlotinib on pemetrexed.

As noted by all studies and as expected, combination therapy generally had higher toxicity versus either single agent, especially in grade 3-4 neutropenia, though most adverse effects were clinically manageable. Hematologic, hepatic and gastrointestinal disorders were frequent, but they were commonly observed even in monotherapy of either agent.

**Future directions**
Recently, pemetrexed has moved to a predominant use in front-line and maintenance use after platinum-containing induction chemotherapy. Meanwhile, EGFR-TKIs have also shifted to a predominant use in front-line when positive EGFR mutation status was detected. Because of gradual reduction of pemetrexed use in second line and a shifting use guided by EGFR testing, these data of combination of EGFR-TKI with cytotoxic agent was not potentially applicable to the current practice environment. Considering controversial results of phase II studies and current evolving background, a large-scale phase III trial of this combination strategy is hesitated.

Survival benefit and tolerability have been demonstrated when either pemetrexed or erlotinib is administered as single-agent maintenance after platinum-doublet induction chemotherapy [35-38]. They were both approved as maintenance therapy by the US-Food and Drug Administration in 2009 and the European Medicines Agency in 2010, respectively. Three phase II studies have demonstrated the safety of the combined use of these two agents in second-line setting. Thus, we are interested in comparisons of combination maintenance of these two agents with monotherapy maintenance of either agent followed by second-line monotherapy with another agent. We are not aware of ongoing or planning studies of this design.

In conclusions, the add-on effects of erlotinib on cytotoxic drug remain controversial from the results of several phase II studies. Combination of erlotinib with pemetrexed or docetaxel is feasible and tolerable. Thus, this combination treatment is potential in maintenance setting of front-line regimen.

Conflict of interests
The authors declare that they have no competing interests.

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