Combining chemotherapy with EGFR inhibition in advanced NSCLC

The availability of targeted agents has become an invaluable resource in the treatment of advanced NSCLC. In the past decade, the three inhibitors of the epidermal growth factor receptor (EGFR; erlotinib, gefitinib and afatinib) have been developed and dramatically changed the outcome of patients with EGFR mutant NSCLC. To date, a total of 9 clinical trials have come to similar results with EGFR TKIs in the first line treatment of NSCLC patients. All these trials illustrate that there is still room for improving the OS of these patients. One strategy to improve this OS that was extensively studied is combining EGFR TKIs with chemotherapy. During a controversy session at the 2014 European Lung Cancer Conference an elaborate overview was given on the different ways of combining EGFR TKIs with chemotherapy.

Concurrent chemotherapy and EGFR inhibition

Four randomized studies comparing the concurrent combination of EGFR-TKIs and platinum-based doublet chemotherapy with chemotherapy alone (Table 1). These studies clearly show that the combination failed to improve the tumor response rate and the survival. A meta-analysis (N=3,918) that included the data of these four studies reinforces this observation as no statistical difference in median OS (10.6 versus 11.0 months, HR[95%CI]: 1.04[0.96–1.13]; p=0.348) was found. However, the PFS was marginally prolonged from 5.4 to 5.6 months (p=0.03). Overall, the current data suggest that concurrent administration of chemotherapy and EGFR-TKI in an unselected population is not a standard therapy for lung cancer.

Intercalated chemotherapy and EGFR inhibition

The failure of the concurrent EGFR TKI chemotherapy trials fed the hypothesis that concurrent administration may not work for the reason of TKI-induced, G1-phase cell-cycle arrest. During the arrest, cell-cycle phase-dependent chemotherapeutic agents will not be effective. By giving EGFR and chemotherapy sequentially and thus achieving pharmacodynamic separation of the two agents, the mutual inhibitory effect could be avoided. A phase I study on sequential administration of pemetrexed followed by erlotinib provided support for the hypothesis. This concept was further tested in the phase II FASTACT trial. A total of 154 treatment-naïve Asian NSCLC patients were randomized to receive gemcitabine plus cisplatin or carboplatin at day 1 and gemcitabine at day 8 followed by erlotinib from days 15 to 28 or similar chemotherapy followed by placebo. The primary endpoint of non-progression rate at 8 weeks was similar for both study arms. However, PFS was significantly longer in the combination arm compared with patients treated with chemotherapy and placebo (7.2 vs. 5.5 months; HR:0.57; p=0.018). Moreover, the tumor response rate was also higher (36.8% versus 24.4%; p=0.12) with the sequential TKI-chemotherapy combination. The encouraging data from FASTACT formed the basis for the randomized, phase III FASTACT II study. In total, 451 patients were randomly assigned to receive six cycles of gemcitabine plus platinum with intercalated erlotinib (N=226) or placebo (n=225) every 4 weeks. The median PFS was significantly prolonged in the erlotinib plus chemotherapy compared with patients treated with chemotherapy and placebo (7.6 vs. 6.0 months; HR[95%CI]: 0.57[0.47-0.69]; p<0.0001). Interestingly. The median OS for patients in the chemotherapy plus erlotinib arm was 18.3 months compared with 15.2 months in the chemotherapy plus placebo group (HR[95%CI]: 0.79[0.64–0.99]; p=0.0420). This benefit in OS for chemotherapy plus erlotinib was observed despite the high rate of cross-over (85%) from patients in the chemo plus placebo arm to a 2nd line EGFR TKI. Not surprisingly, the treatment benefit was only seen in patients

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Chemo</th>
<th>EGFR TKI</th>
<th>RR (%)</th>
<th>PFS (months)</th>
<th>OS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTACT 1</td>
<td>1093</td>
<td>Cisplatin/gemcitabine</td>
<td>Gefitinib 250mg</td>
<td>51.2% vs. 50.3% vs. 47.2%</td>
<td>5.8</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gefitinib 500mg</td>
<td></td>
<td>5.5</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td>6</td>
<td>10.9</td>
</tr>
<tr>
<td>INTACT 2</td>
<td>1037</td>
<td>Carboplatin/paclitaxel</td>
<td>Gefitinib 250mg</td>
<td>30.4% vs. 30.0% vs. 28.7%</td>
<td>5.3</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gefitinib 500mg</td>
<td></td>
<td>4.6</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td>5</td>
<td>9.9</td>
</tr>
<tr>
<td>TALENT 12</td>
<td>1172</td>
<td>Carboplatin/paclitaxel</td>
<td>Erlotinib</td>
<td>28.2% vs. 30%</td>
<td>5.6</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.4</td>
<td>9.9</td>
</tr>
<tr>
<td>TRIBUTE 13</td>
<td>1059</td>
<td>Cisplatin/gemcitabine</td>
<td>Erlotinib</td>
<td>19.3% vs. 21.5%</td>
<td>4.9</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.1</td>
<td>10.8</td>
</tr>
</tbody>
</table>
Table 2. Overview of phase III trials assessing the concurrent combination of EGFR inhibition and chemotherapy.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Log [Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV. Random. 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR-mutation positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB 30406 (2012)</td>
<td>-0.178</td>
<td>0.335</td>
<td>8.3%</td>
<td>0.84 [0.43, 1.61]</td>
</tr>
<tr>
<td>FASTACT-II (2013)</td>
<td>-1.3871</td>
<td>0.2273</td>
<td>11.4%</td>
<td>0.25 [0.16, 0.39]</td>
</tr>
<tr>
<td>INTACT 1 and 2</td>
<td>-0.5954</td>
<td>0.5436</td>
<td>4.6%</td>
<td>0.55 [0.19, 1.60]</td>
</tr>
<tr>
<td>TALET (2007)</td>
<td>-0.5239</td>
<td>0.529</td>
<td>4.8%</td>
<td>0.59 [0.21, 1.67]</td>
</tr>
<tr>
<td>TRIBUTE (2005)</td>
<td>-0.7136</td>
<td>0.4571</td>
<td>5.8%</td>
<td>0.49 [0.20, 1.20]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>34.9% 0.48 [0.28, 0.83]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.23, Chi² = 10.22, df = 4 (P = 0.04), I² = 61%. Test for overall effect: Z = 2.61 (P = 0.009)

| **EGFR-mutation negative** |                    |     |        |                               |
| FASTACT-II (2013) | -0.0318            | 0.1731 | 13.1%  | 0.97 [0.69, 1.36]             |
| Hirsh et al. (2011)| -0.2471            | 0.2276 | 11.4%  | 0.78 [0.50, 1.22]             |
| INTACT 1 and 2    | -0.3125            | 0.1645 | 13.4%  | 0.73 [0.53, 1.01]             |
| TALET (2007)      | -0.0545            | 0.1692 | 13.3%  | 0.95 [0.68, 1.32]             |
| TRIBUTE (2005)    | -0.2216            | 0.1476 | 13.9%  | 0.80 [0.60, 1.07]             |
| Subtotal (95% CI) |                    |       |        | 65.1% 0.84 [0.72, 0.98]       |

Heterogeneity: Tau² = 0.00, Chi² = 2.09, df = 4 (P = 0.72); (2 = 0%. Test for overall effect: Z = 2.25 (P = 0.02)

Test for subgroup differences: Chi² = 3.71, df = 1 (P = 0.05), I² = 73.1%

The clinical benefit of EGFR mutation positive patients was taken into account, a different picture was revealed. In 4,585 patients with EGFR mutation positive NSCLC. However, the best schedule (timing, sequence, etc.) of TKI and chemotherapy delivery is still largely unknown. Further studies to shed more light on this are therefore warranted.

Conclusions

A recently published meta-analysis grouped the data of eight clinical trials comparing chemotherapy plus an EGFR TKI with chemotherapy alone (CALGB 30406, FASTACT, FASTACT II, Hirsh et al, INTACT 1, INTACT 2, TAIENT, TRIBUTE). Meta-analysis, including 4,585 patients revealed that the chemotherapy – EGFR TKI combination was associated with a significantly longer PFS (HR[95%CI]: 0.81 [0.69-0.95]). Unfortunately, this did not translate into a longer statistically longer OS (HR[95%CI]: 1.01 [0.93-1.08]). However, when the EGFR mutation status was taken into account, a different picture was revealed. In fact, the effect in EGFR mutation negative NSCLC patients was similar to what was seen in the unselected population (HR for PFS 0.84[0.72-0.98) and for OS 0.91[0.72-1.08]), but in EGFR mutation positive patients the clinical benefit of the combined treatment strategy was much more pronounced with a HR for PFS of 0.48[0.28-0.83]. Moreover, this translated into a HR for OS of 0.67 [0.44-1.00] (Table 2).

As such, these data indicate that chemotherapy should form a significant component of treatment in patients with EGFR mutation positive NSCLC. However, the best schedule (timing, sequence, etc.) of TKI and chemotherapy delivery is still largely unknown. Further studies to shed more light on this are therefore warranted.

References

Overcoming resistance to EGFR tyrosine kinase inhibitors

EGFR mutation testing has become part of the routine work-up of NSCLC cases and EGFR TKIs have dramatically changed the course of the disease. Nevertheless, practically all patients treated with EGFR TKIs progress within 1 year due to the development of acquired resistance.1-3 This acquired resistance can be the result of additional genetic alterations in the EGFR gene (most commonly T790M mutation), amplification of the MET gene, or by EGFR independent mechanisms (e.g. activation of downstream signaling pathways, etc.).4,6 Once EGFR-mutant patients acquire resistance during the course of an EGFR TKI, no optimal therapy has been established and there are no clinical data to provide guidance on what criteria should be used to change treatment.

Continue TKI with or without chemotherapy, or local therapy

Given the indolent nature of EGFR-mutant cancers, patients are sometimes treated with EGFR TKI beyond RECIST-defined progression if there is no clinical evidence of deterioration or intolerable toxicity.7 In fact, a cohort study demonstrated continuing EGFR TKI beyond progression can delay the introduction of systemic therapy by more than 12 months in 19% of patients.8 Switching to chemotherapy after disease progression on EGFR TKIs does not seem to be the best option. In fact, a meta-analysis of phase III trials evaluating the use of 2nd line chemotherapy in EGFR mutant patients revealed a response rate of only 28.8%.9 Moreover, disease flare, a phenomenon of rapid disease progression during a TKI ‘washout period’, is observed in 23% of patients, with a median time to flare of 8 days after TKI cessation.10 This fact has led many clinicians to continue TKI therapy along with chemotherapy over chemotherapy alone, but this strategy has not yet been fully explored. Nevertheless, combining chemotherapy with EGFR inhibition is in line with the hypothesis that patients with acquired EGFR TKI resistance harbour heterogeneous tumors with both TKI sensitive and TKI resistant cell populations. By combining targeted therapy with a systemic approach both cell populations could be attacked. Two large phase III clinical trials are assessing this treatment strategy (ASPIRATION, IMPRESS) and results of both trials are expected later this year. As discussed in another article in this congress news oncology edition, combining TKIs with local therapy may also be a feasible treatment option for patients with oligo-progressive NSCLC.

Second and third line EGFR TKIs

Preclinical studies with second line, irreversible EGFR TKIs indicated that these TKIs were able to overcome T790M mediated resistance.11 However, this could not be replicated in clinical trials where disappointing response rates were reported. Currently, several third generation EGFR TKIs are under development (CO1686, AZD9291, HM61713). Early phase I data with these agents are promising and they will soon enter phase II/III development.

Combining targeted agents

Based on the mechanisms of primary and acquired resistance in EGFR-mutant NSCLC, several rational combinations have been tested in preclinical models, but rendered disappointing phase I results. Probably the most promising combination consists of afatinib plus cetuximab. In a study by Janjigian et al, an overall response rate of 40% was reported with this combination in NSCLC patients with acquired resistance to erlotinib or gefitinib.12 As such, this combination deserves further evaluation.

References

Tyrosine kinase inhibitors (TKIs) targeting the epidermal growth factor receptor (EGFR) in EGFR mutated NSCLC patients have revolutionized the clinical management of these patients by significantly prolonging the progression free survival (PFS) and increasing the radiographic response rate.1-3 Nevertheless, despite the initial success of these agents, all patients eventually progress, with a median PFS of 12–16 months.1-3 Acquired resistance to EGFR TKIs has been attributed to several molecular mechanisms. The most common etiologies of resistance are the development of the T790M missense mutation.4 Notwithstanding this acquired resistance to first line EGFR TKI, continued EGFR inhibition appears to provide continued clinical benefit.5 Moreover, withdrawing the EGFR TKI at progression leads to disease flare in a significant proportion of patients (23%).6 These data suggest that the ‘TKI resistant’ tumor is still EGFR oncogene dependent and indicate the coexistence of EGFR TKI sensitive and resistant tumor clones in the tumor. As such, these data form the rationale for continued TKI EGFR therapy combined with local therapy in patients with oligo-progressive NSCLC.

Local therapies including radiation, radiofrequency ablation, and metastasectomy are established treatment strategies in certain cancers including renal cell carcinoma, sarcoma, and colorectal cancer. Such approaches are now recommended in the NCCN guidelines for oligometastatic disease.7,8 Nevertheless, local therapy is not commonly used in metastatic lung cancer. However, recent studies from Yu et al. and Weickhardt et al. demonstrate that combining local therapy with continued TKI treatment form a feasible treatment option in patients with oligo-progressive NSCLC.

In the study by Yu et al., 18 patients received local therapy and restarted TKI therapy within 1 month. The median time to progression after local therapy was 10 months while the median time until a subsequent change in systemic therapy was 22 months.9 Similarly, Weickhardt et al. studied patients with either ALK or EGFR mutations who were subsequently treated with crizotinib or erlotinib. When these TKI drugs were given as initial therapy, the PFS with crizotinib was 9.0 months, and 13.8 months for patients treated with erlotinib. In total, 51 patients experienced disease progression of whom 25 were suitable for local ablative therapy with either radiotherapy or surgery along with continuation of the same TKI therapy. The median time to the second progression was 6.2 months in addition to the previous period of PFS achieved with frontline TKI therapy.10

Conclusion
These two studies indicate that local therapy for oligo-metastatic disease combined with continued TKI treatment can be a useful treatment option for NSCLC patients with acquired resistance to an EGFR TKI. In fact, these local therapies can usually be performed with minimal toxicity and result in several months to years of disease control. As such, these recommendations have recently been included in the updated NCCN guidelines for the management of NSCLC.11 The advent of next generation kinase inhibition will probably lead to a modification of this strategy. However, till that day combining local therapy with continued EGFR inhibition is the preferred treatment option for patients with oligo-progressive, EGFR mutant NSCLC.

References