Erlotinib in the Treatment of Non-small Cell Lung Cancer: Current Status and Future Developments

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Abstract. Erlotinib is an orally small molecule inhibiting the tyrosine kinase activity of the epidermal growth factor receptor (EGFR). Currently, erlotinib, at a standard oral daily dose of 150 mg, is licensed for the treatment of unselected recurrent non-small cell lung cancer (NSCLC) patients, however, it is being investigated in all stages of NSCLC. Erlotinib is well tolerated, with common toxicities including rash and diarrhoea. The optimization of the therapeutic impact of erlotinib in NSCLC will be more defined when reliable predictive factors are identified. An important step has been made in the molecular characterization of potentially sensitive NSCLC patients. In fact, we have learned that activation, somatic EGFR gene mutations within the tyrosine kinase domain, are associated with a high possibility of a long lasting therapeutic response to erlotinib. The present review discusses the role of erlotinib in the treatment of NSCLC.

Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancer diagnoses (1). The majority of people diagnosed with NSCLC are unsuitable for surgery since most patients have advanced disease at diagnosis. In recent decades, conventional treatments (surgery, chemotherapy, radiotherapy) have apparently reached a plateau of effectiveness in improving the outcomes of NSCLC patients, which still remain disappointing, especially in advanced stages (2), hence new treatment approaches have been developed.

The epidermal growth factor receptor (EGFR) is one of the most studied targets for cancer therapy. The present review discusses the role of erlotinib, an anti-EGFR tyrosine kinase inhibitor (TKI), in the treatment of NSCLC.

Epidermal Growth Factor Receptor Pathway

The EGFR, also known as ErbB-1/HER1, is the first of four members of the ErbB family of cell membrane receptors, which are important mediators in cell growth, differentiation, and survival (3, 4). The EGFR is known to bind with a high affinity to several ligands including EGF, amphiregulin and transforming growth factor α (TGFα). NSCLC is characterized by a generally high expression, about 40-80%, of the EGFR family members of ligands and receptors (5).

Two classes of EGFR antagonists have been successfully tested in phase III trials: anti-EGFR monoclonal antibodies (for example cetuximab) and small-molecule EGFR-TKIs (for example gefitinib and erlotinib). Both these two small molecules are administered orally, daily and inhibit EGFR activity by competing with adenosine triphosphate (ATP) for the ATP-binding site localized on the EGFR intracellular domain. The antitumour effects of EGFR inhibition in human cancer models are: inhibition of cancer cell proliferation with G0/G1 cell cycle arrest and, in some cases, induction of apoptosis; anti-angiogenesis through inhibition of angiogenic growth factor production; inhibition of invasion and metastases; potentiation of antitumour activity of cytotoxic drugs and of radiotherapy (5).

Several retrospective and prospective analyses revealed prognostic/predictive clinical and molecular factors related to the treatment with EGFR-TKIs, gefitinib and erlotinib (6, 7). In fact, the clinical predictors of response to EGFR-TKIs included female gender, adenocarcinoma histology, Asian ethnicity and particularly a history of never-smoking. The molecular predictors of activity are EGFR overexpression detected by immunohistochemistry (IHC), EGFR gene copy
number detected by fluorescence in situ hybridization (FISH), EGFR and Kras mutational status which all seem to influence the outcomes (Table I) (6, 7). EGFR mutations in exons 18 through 21 have been reported to be the most important prognostic/predictive molecular factors for NSCLC and TKI therapy (8, 9).

The most common toxicity related to treatment with EGFR-TKIs is skin rash and diarrhoea, which are dose-limiting. The positive relationship between the development of rash and response and/or survival, which has been shown in erlotinib clinical trials, makes the occurrence of skin reactions a potential surrogate marker for anti-EGFR drug efficacy (10).

**Early Stage NSCLC**

Early stages of NSCLC, including stages I-III A, are diagnosed in about 20% of patients. These stages of disease are amenable to surgery, with 5-year survival rate ranging from 67% (stage I) to 23% (stage III A) (11). In patients with pathological stages, II-III A, adjuvant chemotherapy with cisplatin-based regimens is the standard approach, improving the 5-year survival absolute benefit by about 5%. In stage III A, radiotherapy is not recommended for routine use due to the lack of prospective randomized clinical trial data evaluating its efficacy (12).

Erlotinib is being employed in completely resected NSCLC patients with the aim to improve the outcome. In fact, the RADIANT (Randomized Double-blind Trial In Adjuvant NSCLC with Tarceva) study is a phase III trial comparing erlotinib 150 mg daily versus placebo (2:1) in stage IB-III A NSCLC patients with EGFR-positive tumours (IHC and/or FISH), following complete surgical resection and up to 4 cycles of adjuvant chemotherapy. Planned accrual is 945 patients and primary endpoint is disease-free survival (DFS). Preliminary data concerning biomarker analysis have been reported. Among the 655 analysed tissue samples, 96% were EGFR IHC-positive and 74% EGFR FISH-positive. Of the 476 tissue samples analysed to date for mutations, 12% had activating EGFR and 19% had KRAS mutations. Preliminary comparisons suggest that EGFR mutation rate increased while KRAS mutation rate decreased with tumour stage. Once complete, this study will provide a robust biomarker dataset on which to evaluate predictive and prognostic response markers, which may help determine who may benefit from treatment with erlotinib in the adjuvant setting (13).

Another ongoing trial, named TASTE (Tailored post-Surgical Therapy in Early stage NSCLC), is a phase II/III randomised study in which patients affected by stage II-III A non-squamous NSCLC which have been radically resected are randomized either to standard arm, consisting of cisplatin plus pemetrexed, or to experimental arm, consisting of erlotinib or cisplatin plus pemetrexed, or to observation, in which the choice of treatment depends on the EGFR mutational status and ERCC-1 (excision repair cross-complementation group 1) expression. The primary endpoint is feasibility and the secondary is DFS (14).

A retrospective review of patients with resected stage I-III lung adenocarcinoma harbouring EGFR exon 19 or 21 mutations, some of whom received EGFR TKIs postoperatively, was performed. A total of 167 patients were identified, 53 of whom received either adjuvant erlotinib or gefitinib. The median DFS was 43 months in the group that received a TKI versus 31 months for the one which did not. The 2-year DFS was 88% (77% in non-TKI group). After controlling for stage of disease, individuals who received adjuvant gefitinib or erlotinib had a better DFS (hazard ratio [HR]=0.38, 95% confidence interval [CI], 0.16-0.90) than the non-TKI group (p=0.03). The 2-year overall survival (OS) was 95% (86% in the non-TKI group). The median OS was not reached (15). These data indicate that the adjuvant use of either gefitinib or erlotinib improves DFS in patients with completely resected stage I-III lung adenocarcinomas with mutations in EGFR exons 19 and 21, thus justifying a prospective randomized trial in this setting.

**Locally Advanced NSCLC**

Locally advanced NSCLC stages represent about 25% of new diagnoses. This group includes unresectable stages III A-IIIB, and combinations of chemotherapy and radiotherapy are currently the standard treatment approach for this setting.

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### Table I. Clinical and biological prognostic and predictive factors of EGFR-TKIs in advanced non-small cell lung cancer.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical factors*</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>No absolute prognostic/predictive role</td>
</tr>
<tr>
<td>Asian ethnicity</td>
<td>No absolute prognostic/predictive role</td>
</tr>
<tr>
<td>Adenocarcinoma histology</td>
<td>No absolute prognostic/predictive role</td>
</tr>
<tr>
<td>Never smoker status</td>
<td>No absolute prognostic/predictive role</td>
</tr>
<tr>
<td>Biological factors</td>
<td></td>
</tr>
<tr>
<td>EGFR protein expression</td>
<td>No role</td>
</tr>
<tr>
<td>EGFR gene copy number</td>
<td>No role</td>
</tr>
<tr>
<td>EGFR mutations</td>
<td>Positive prognostic factor for survival</td>
</tr>
<tr>
<td></td>
<td>Positive predictive factor for EGFR TKIs efficacy</td>
</tr>
<tr>
<td>KRAS mutations</td>
<td>Negative prognostic factor for survival</td>
</tr>
<tr>
<td></td>
<td>No role as predictive factor for EGFR TKI efficacy</td>
</tr>
</tbody>
</table>

*Clinical factors in which a higher incidence of EGFR mutations has been detected; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors.
Concomitant chemo-radiotherapy, although associated with increased acute toxicity, has been demonstrated to be the better strategy over sequential chemoradiotherapy and it is to be considered a standard approach in patients with good performance status (PS) (16). The locally advanced disease includes several and high heterogeneous stages, as demonstrated by the 5-year survival rate, which ranges from 3 to 13% (11). Notwithstanding the progresses reported in the treatment of locally advanced NSCLC obtained by combining chemotherapy with radiotherapy, treatment outcomes in this clinical setting are still to be considered disappointing.

Data concerning only a few cases involving the introduction of erlotinib in the multimodality treatment of locally advanced NSCLC are available, most of which report only preliminary results. The only study reporting final results is a phase I study aimed to determine the maximum-tolerated dose (MTD) of erlotinib administered with two standard chemoradiotherapy regimens (17).

A randomised phase II feasibility trial evaluated the addition of erlotinib to radiotherapy in patients with unresectable stage I-IIIA NSCLC not suitable for chemotherapy. Preliminary results on 23 evaluable patients (10 receiving radiotherapy and 13 radiotherapy plus erlotinib) showed that the addition of erlotinib did not appear to increase in-field toxicities, thus improving the control of disease (18).

Another interesting trial investigated the combination of erlotinib and bevacizumab, an antivascular endothelial growth factor (VEGF) monoclonal antibody, in combination with chemo-radiotherapy in stage III NSCLC. The primary endpoint was progression-free survival (PFS) at 1 year. All histologies were studied including squamous cell carcinoma. Overall response rate (OR) following treatment in the 31 evaluable patients was 68.2% (95% CI, 45-86%). The PFS at 1 year was 58% (95% CI, 34-76%), with a promising estimated 1-year survival of 79% (19).

**Metastatic Stage NSCLC**

It is estimated that about 50% of all patients are at metastatic stage at the time of diagnosis of their disease. Chemotherapy is the cornerstone for the treatment of metastatic NSCLC, while radiotherapy has only a palliative role. Unfortunately the prognosis is very poor, with a 5-year survival < 1% (11). Erlotinib has been investigated in metastatic NSCLC as first-, second- and third-line therapy and as maintenance treatment.

**First-line therapy.** Erlotinib in combination with chemotherapy for the first-line treatment of NSCLC has been evaluated in two large multicentre randomised placebo-controlled clinical trials. In the TRIBUTE (Tarceva Responses in Conjunction with Paclitaxel and Carboplatin) study, 1,059 patients with untreated advanced stage IIIB/IV NSCLC were randomised to receive carboplatin plus paclitaxel with or without erlotinib 150 mg daily. Median OS for patients treated with erlotinib was 10.6 versus 10.5 months for placebo (HR 0.99; p=0.95, 95% CI, 0.86-1.16), OR was similar for both the erlotinib and the placebo arm (21.5% versus 19.3%, respectively; p=0.36), time-to-progression (TTP) was 5.1 months for erlotinib and 4.9 months for placebo (HR 0.937; p=0.36). Patients who were reported as never smokers (72 erlotinib; 44 placebo) experienced improved OS in the erlotinib arm (22.5 versus 10.1 months for placebo; HR 0.49, 95% CI, 0.28-0.85; p=0.01). The median TTP in never smokers was also improved by the administration of erlotinib, being 6.0 versus 4.3 months for the placebo arm (HR 0.50) (20).

In the TRIBUTE trial, among erlotinib-treated patients, **EGFR** mutations were associated with improved OR (53% versus 18% for the placebo arm; p<0.05) and there was a trend toward an erlotinib benefit on TTP (12.5 versus 6.6 for placebo group; p=0.092), but it did not improve OS (p=0.96) (21). As a result, this analysis revealed that **EGFR** mutations may be a positive prognostic factor for OS in advanced NSCLC patients treated with chemotherapy with or without erlotinib, and may predict greater likelihood of response to erlotinib. In the TALENT (Tarceva Lung Cancer Investigation Trial) study 1,172 patients were randomised (586 per each arm) to receive cisplatin plus gemcitabine, with or without erlotinib 150 mg daily. In this trial there was also no statistically significant difference in any outcome, with median OS of 43 versus 44.1 weeks for the erlotinib and the placebo groups, respectively (HR 1.06). The subgroup analyses were performed on a very small number of patients, and only those who had never smoked had an increased OS reported; no other subgroups were found more likely to benefit from treatment (22).

The effect of smoking was examined in the TRIBUTE trial. Despite a lack of benefit in the overall patient population, when the analysis was confined to those who had never smoked, erlotinib seemed to provide an OS benefit (median OS of 10 and 22.5 months, for smokers and never-smokers, respectively; p=0.01) (20). In the TALENT study, smoking history was collected retrospectively, and was available for a small number of patients. Median OS in never-smokers (n=10) was 11.4 months with placebo, but was not reached with erlotinib (n=8). Median PFS was longer with erlotinib (7.9 months) than with placebo (5.4 months; HR 0.195; p=0.02) (23).

Table II summarizes the results of phase III trials employing erlotinib plus chemotherapy as first-line treatment of advanced NSCLC.

Overall, there was no clinical benefit in either trial, and currently concurrent use of erlotinib with chemotherapy is not recommended in the first-line treatment of NSCLC. However, erlotinib has been investigated in conjunction with chemotherapy but with a different combination method. A
A phase II randomised trial evaluated whether sequential administration of erlotinib and chemotherapy improves clinical outcomes versus chemotherapy alone in unselected, chemotherapy-naive patients with advanced NSCLC. A total of 154 patients were randomly assigned to either receive erlotinib, 150 mg daily, or placebo on days 15 to 28 of a 4-week cycle that included gemcitabine and either cisplatin or carboplatin. The nonprogression rate at 8 weeks, primary endpoint, was 80.3% in the gemcitabine plus platinum-erlotinib arm (n=76) and 76.9% in the chemotherapy-placebo arm (n=78). At 16 weeks, the nonprogression rate was 64.5% versus 53.8%, respectively. The OR was 35.5% versus 24.4%, median PFS was 29.4 versus 23.4 weeks (HR, 0.47; p=0.0002), respectively. There was no significant difference in OS with 74.1 weeks for the erlotinib arm and 75.7 weeks for the placebo arm (HR1.09, 95% CI, 0.70-1.69; p=0.42). Of interest is the fact that regardless of the treatment received, never smokers (median not reached; 95% CI, 85.7 weeks) had longer OS than ever smokers (median, 57.9 weeks; 95% CI, 42.7-75.1 weeks; p<0.0001). The addition of erlotinib to chemotherapy was well tolerated, with no increase in hematological toxicity (23). Thus, this method of combining erlotinib and chemotherapy should be further investigated.

Several phase II trials investigating erlotinib as a single-agent in the first-line setting in unselected NSCLC patients have been performed, reporting OR and OS values comparable with those expected after conventional chemotherapy (10, 24, 25). Based on these results, our group launched the Italian-Canadian trial TORCH (Tarceva or Chemotherapy), a phase III randomized multicenter study based on a non-inferiority OS comparison between an experimental strategy including first-line erlotinib followed at progression by chemotherapy with cisplatin and gemcitabine, or the inverse sequence as standard arm. This trial will allow the relationship between molecular predictors, such as *EGFR* and *KRAS* mutational status, and erlotinib treatment response to be studied. The aim

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>OR (%)</th>
<th>TTP (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIBUTE, 2005 (20)</td>
<td>CBDCA + PAC + Placebo vs. erlotinib</td>
<td>533</td>
<td>19.3</td>
<td>10.5</td>
<td>4.9</td>
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<tr>
<td></td>
<td>CBDCA + PAC + Placebo vs.</td>
<td>526</td>
<td>21.5</td>
<td>10.6</td>
<td>5.1</td>
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<tr>
<td>TALENT, 2007 (22)</td>
<td>CDDP + GEM + Placebo vs.</td>
<td>586</td>
<td>29.9</td>
<td>24.6*</td>
<td>44.1*</td>
</tr>
<tr>
<td></td>
<td>CDDP + GEM + Placebo vs.</td>
<td>586</td>
<td>31.5</td>
<td>23.7*</td>
<td>43*</td>
</tr>
</tbody>
</table>

*Weeks; OR=response rate; TTP=time-to-progression; OS=overall survival; CBDCA=carboplatin; PAC=paclitaxel; CDDP=cisplatin; GEM=gemcitabine.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>OR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SATURN, 2009 (34)</td>
<td>Placebo vs. erlotinib</td>
<td>451</td>
<td>5</td>
<td>HR 0.71</td>
<td>HR 0.81</td>
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<tr>
<td></td>
<td>Placebo vs.</td>
<td>438</td>
<td>12</td>
<td>HR 0.71</td>
<td>HR 0.81</td>
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<tr>
<td>ATLAS, 2009 (38, 39)</td>
<td>Bevacizumab + Placebo vs. erlotinib</td>
<td>373</td>
<td>NR</td>
<td>3.75</td>
<td>NR</td>
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<tr>
<td></td>
<td>Bevacizumab + Placebo vs.</td>
<td>370</td>
<td>NR</td>
<td>4.76</td>
<td>NR</td>
</tr>
</tbody>
</table>

OR=Response rate; PFS=progression-free survival; OS=overall survival; HR=hazard ratio; NR=not reported.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>OR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BR.21, 2005 (40)</td>
<td>Placebo vs. erlotinib</td>
<td>243</td>
<td>&lt;1</td>
<td>2.2</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>Placebo vs.</td>
<td>488</td>
<td>8.9</td>
<td>1.8</td>
<td>6.7</td>
</tr>
<tr>
<td>BeTa Lung, 2008 (46)</td>
<td>Erlotinib + Placebo vs. Bevacizumab</td>
<td>317</td>
<td>6.2</td>
<td>1.7</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>Erlotinib + Bevacizumab</td>
<td>319</td>
<td>12.6</td>
<td>3.4</td>
<td>9.3</td>
</tr>
</tbody>
</table>

OR=Response rate; PFS=progression-free survival; OS=overall survival.
of the TORCH study is to evaluate, in a randomised fashion, which is the most appropriate and cost-effective sequential approach for erlotinib and chemotherapy in an unselected advanced NSCLC (26).

On the other hand, phase II trials have investigated erlotinib in patients selected for prognostic/predictive clinical and molecular factors. In fact, erlotinib has been administered as first-line therapy, within phase II trials, in patients having at least one of the clinical factors predictive of EGFR-TKI activity, i.e., in adenocarcinoma and bronchioloalveolar carcinoma (27), never-smokers (28), female gender (29), and Asians (30). Overall, the results reported better outcomes in respect to those reported in the unselected patient population. However, analysing where possible the molecular factors, in most of the responsive patients, EGFR mutations were detected, which as stated before are represented mainly in patients with the reported clinical characteristics (8, 9).

A retrospective analysis combined data from 223 patients who were included in five trials in predominantly Western populations to assess the impact of EGFR and KRAS mutations on first-line therapy with an EGFR-TKI, erlotinib or gefitinib. Clinical versus molecular predictors of sensitivity were compared. Sensitising EGFR mutations were associated with a 67% OR, TTP of 11.8 months, and OS of 23.9 months. Exon 19 deletions were associated with longer median TTP and OS compared with L858R mutations. This means that not only is the presence of EGFR mutations important but also the type of mutation, which could be the strongest predictive factor of EGFR-TKI activity. Wild-type EGFR was associated with poorer outcomes (OR, 3%; TTP, 3.2 months) irrespective of KRAS status. No difference in outcome was seen between patients harbouring KRAS transition versus transversion mutations. EGFR genotype was more effective than clinical characteristics at selecting appropriate patients for consideration of first-line therapy with an EGFR-TKI (31).

Recently, a prospective large phase II trial reported very interesting results about the use of erlotinib in advanced NSCLC patients harbouring EGFR mutations. In this trial, the feasibility of large-scale screening for EGFR mutations in such patients was evaluated by analysing the association between the mutations and the outcome of the erlotinib treatment. The patients screened for EGFR mutations were 2,105 and only 350 (16.6%) harboured them. Mutations were more frequent in women (69.7%), in patients who had never smoked (66.6%), and in those with adenocarcinomas (80.9%) (p<0.001 for all comparisons). The mutations were deletions in exon 19 (62.2%) and L858R (37.8%). Median PFS and OS for 217 patients (113 as first-line and 104 as second- or third-line therapy) who received erlotinib were 14 and 27 months, respectively. The adjusted HR for the duration of PFS were 1.92 for the presence of the L858R mutation, as compared with a deletion in exon 19 (p=0.02); and 1.68 for the presence of the L858R mutation as compared with the absence of the mutation (p=0.02). Grade 3 skin toxicity was recorded in 16 patients (7.4%) and grade 3 diarrhoea in 8 patients (3.7%) (32). These results confirmed those reported, mainly retrospectively, concerning the role of EGFR mutations in the treatment with EGFR-TKIs; patients harbouring sensitising EGFR mutations should be considered for first-line erlotinib or gefitinib. A phase III trial comparing erlotinib with platinum-based chemotherapy in NSCLC patients harbouring EGFR mutations in Western countries as first-line therapy is ongoing (14).

Maintenance treatment. Maintenance treatment is the prolongation of treatment duration with the administration of additional drugs at the end of a defined number of initial chemotherapy cycles, after achieving tumour control in an individual patient (33).

The phase III trial named SATURN (Sequential Tarceva in Unresectable Lung Cancer) was a randomized clinical study set up to determine whether erlotinib is effective as maintenance therapy in advanced NSCLC. A total of 889 patients with no evidence of disease progression after 4 cycles of chemotherapy were randomised to receive either erlotinib 150 mg/day or placebo until progression or unacceptable toxicity. The primary endpoint was PFS in all patients and the co-primary endpoint was PFS in EGFR IHC-positive patients. PFS was significantly prolonged with erlotinib versus placebo in all patients (HR 0.71, 95% CI, 0.62-0.82; p=0.000003) and in EGFR IHC-positive patients (HR 0.69, 95% CI, 0.58-0.82; p=0.00002). All biomarker subgroups showed a PFS benefit with erlotinib, including patients whose tumours had wild-type EGFR (HR 0.78, 95% CI, 0.63-0.96; p=0.0285). In particular, the EGFR mutation status (exon 19 deletions and/or L858R) was associated with a marked improvement in PFS with erlotinib therapy (HR 0.10, 95% CI, 0.04-0.25; p<0.0001). KRAS mutation status was a prognostic factor but did not affect the clinical benefit seen with erlotinib. Median OS was statistically significantly superior for all the population in the erlotinib arm (HR 0.81). It was superior both in patients with non-squamous histology (HR 0.79) and patients with EGFR wild-type (HR 0.77, 95% CI, 0.61-0.97; p=0.0243). Median OS was not reached in patients with EGFR mutations (HR 0.83) and there was a 67% of these patients, randomized in the placebo arm, who received a second-line EGFR-TKIs. OR was 12% with erlotinib versus 5% with placebo. The disease control rate (complete response + partial response + stable disease > 12 weeks) was 40.8% with erlotinib versus 27.4% with placebo (p=0.0001). Quality of life (QoL) was similar in both arms. Erlotinib significantly extended time to pain (HR 0.61; p=0.008) and time to analgesic use (HR 0.66; p=0.0199). Erlotinib was well tolerated: the majority of treatment-related adverse events were grade 1/2. Overall, the SATURN study
met its primary and co-primary endpoints with high statistical significance. The survival benefit was particularly large in patients with adenocarcinoma histology and was not driven by the EGFR mutation-positive subgroup, with a significant improvement in survival also observed in the EGFR wild-type group (34, 35).

A functional relationship between the EGFR signalling pathway and the VEGF pathway exists (36), suggesting that a dual blockade of these targets may produce additive and/or synergistic antitumor effects. On this rational basis, several preclinical studies have evaluated the activity of combined anti-EGFR and anti-VEGF drugs (37).

Based on these data, the combination of erlotinib and bevacizumab has been studied as maintenance treatment. In fact, the ATLAS trial, a global, multicentre, randomised, double-blind, placebo-controlled study, involved 743 patients with advanced NSCLC who were treated with 4 cycles of chemotherapy (various platinum-containing doublets) and bevacizumab. Patients who did not progress were then randomized to maintenance therapy with bevacizumab alone or bevacizumab plus erlotinib until progression. The main endpoint was PFS. Grade 3 to 4 adverse events were observed in 44.1% of patients enrolled in the bevacizumab plus erlotinib arm and 30.4% of patients in the bevacizumab only arm. The treatment was well tolerated in both arms. The Data Monitoring Committee recommended stopping the trial at the second planned interim efficacy analysis because it had met the primary endpoint. The results showed a significant increase in median PFS from 3.75 months for bevacizumab alone to 4.76 months for bevacizumab plus erlotinib (HR 0.722, 95% CI, 0.592-0.881; p=0.0012) (38). At the time of this report, the OS data are still not mature. In addition for this trial, a prospective analysis of the prognostic/predictive value of several biomarkers was performed. PFS results suggested that EGFR FISH-positive (HR 0.66, 95% CI, 0.39-1.13), EGFR mutated (HR 0.93, 95% CI, 0.55-1.56), and KRAS wild-type (HR 0.67, 95% CI, 0.49-0.91) patients could derive the greatest improvement with bevacizumab plus erlotinib (39).

Overall, taking into account the results of these two trials, erlotinib could be indicated as a potential drug for use as maintenance first-line therapy (Table III).

**Recurrent NSCLC**

Two randomized phase III trials investigated erlotinib in recurrent NSCLC patients (Table IV). The registrative BR.21 study in which erlotinib was compared with placebo in stage III/IV NSCLC patients who had failed first- or second-line chemotherapy (40). A total of 731 patients were randomized in a 2:1 ratio to receive either erlotinib at 150 mg/day or placebo. These patients had a metastatic NSCLC which had previously been treated with one standard chemotherapy regimen (50% of patients) or with two chemotherapy regimens (50% of patients). Almost all patients received platinum-based chemotherapy. The OR was 8.9% in the erlotinib arm and less than 1% in the placebo group (p<0.001). PFS was 2.2 and 1.8 months, respectively (HR 0.61; p<0.001). The median OS was 6.7 months for those in the erlotinib regimen compared with 4.7 months in the placebo arm (HR 0.7, 95% CI, 0.58-0.85; p<0.001). Based on these results, erlotinib was licensed for the treatment of chemotherapy-resistant advanced NSCLC patients. QoL evaluation, defined as the time for a clinically significant deterioration to occur in three common lung cancer symptoms, showed that patients receiving erlotinib had a significantly longer median deterioration-time for all three symptoms: 4.9 versus 3.7 months for cough (p=0.04); 4.7 versus 2.9 months for dyspnoea (p=0.04); and 2.8 versus 1.9 months for pain (p=0.03) (41).

Several retrospective analyses were performed in the BR.21 study. In this trial, clinical predictors of response included female gender, adenocarcinoma, Asian ethnicity and a history of never-smoking, even though erlotinib had a significant effect on OS in all subgroups of patients (42). In fact, the ORs were more frequent in women (14% versus 6%, p=0.0065), in patients with adenocarcinoma as compared to other histotypes (14% versus 4.1%, p<0.0001), and in patients without smoking history (25% versus 4%, p<0.0001). Despite the fact that male smokers with squamous cell carcinoma have been considered non-ideal candidates for treatment with erlotinib, in this group, the median OS improved significantly among patients receiving erlotinib (n=100) compared with patients with similar characteristics in the placebo arm (n=57) (p=0.016). This difference resulted in a median OS of 5.5 months in the erlotinib arm compared with 3.4 months in the placebo arm (42). Overall, 197 specimens were analysed for EGFR gene mutations which were most commonly identified in exon 19 and 21. A total of 45 EGFR mutations were identified in 23% of the analysed samples. Twenty-one mutations were either deletions in exon 19 or a mutation in exon 21 L858R, whereas 24 were novel mutations. Patients who had a mutation had a higher OR, although this was not statistically significant. There was no significant difference in OS benefit observed in the erlotinib group as compared with the placebo group in patients with exon 19 deletion or exon 21 L858R mutation (p=0.39), nor in patients with novel mutations (p=0.41) (43). Moreover in this trial, high levels of EGFR protein expression were associated with OR and OS in a retrospective subset analysis. In fact, EGFR-IHC positive patients treated with erlotinib had a significantly superior OS compared with placebo treated patients (HR 0.68; p=0.02) (43). In the same trial, 159 tumours were analysed for EGFR gene copy by FISH and 61 (38%) were positive. ORs were 5% for EGFR FISH-negative and 21% for FISH-positive
patients \( (p=0.02) \). Significant OS benefit from the erlotinib therapy was observed for patients with EGFR FISH positivity (HR=0.43; \( p=0.004 \)) but not for patients with EGFR FISH negativity (HR=0.80; \( p=0.35 \)). In multivariate analysis, only EGFR FISH-positive status was prognostic for poorer OS (\( p=0.025 \)) and predictive of differential OS benefit from erlotinib (\( p=0.005 \)). An exploratory analysis of \( KRAS \) mutations status in the BR.21 trial was conducted in 206 patients; 30 (14.6\%) specimens had missense mutations in codon 12 or 13 (22 on the erlotinib arm and 8 on the placebo arm). For all 206 patients with known \( KRAS \) genotype, the HR in the erlotinib was 0.77 (95\% CI 0.57-1.06, \( p=0.06 \)). Significant OS benefit from the erlotinib therapy was observed for the 176 patients with wild-type \( KRAS \) with HR of 0.69. In contrast, the HR for the 30 patients with mutant \( KRAS \) was 1.67, with an interaction \( p \)-value of 0.09. ORs were 5\% (1/20) in \( KRAS \)-mutant patients, and 10.2\% (10/98) in \( KRAS \) wild-type patients. In patients with identified \( KRAS \) genotype, the multivariate Cox regression model showed that \( KRAS \) mutations were strongly associated with shorter OS (HR 1.63) (44).

Cigarette smoking induces CYP1A1/1A2 and is hypothesized to alter erlotinib pharmacokinetics. Cohorts of NSCLC patients currently smoking \( \geq 10 \) cigarettes per day for \( \geq 1 \) year received escalating doses of erlotinib for 14 days until dose-limiting toxicity (DLT). A separate cohort of patients was then randomly assigned to erlotinib at either MTD or 150 mg daily, with pharmacokinetics assessed at day 14. DLT was observed in two out of five patients at 350 mg (acneform dermatitis and fatigue). Thirty-five patients were randomly assigned to 150 mg or 300 mg of erlotinib. Common adverse events (all grades) were: skin toxicity (150 mg, 29\%; 300 mg, 67\%), diarrhoea (150 mg, 18\%; 300 mg, 50\%), fatigue (150 mg, 12\%; 300 mg, 17\%). This trial reported that the MTD of erlotinib in NSCLC patients who smoked was 300 mg. Steady-state trough plasma concentrations and incidence of rash and diarrhoea in smokers at 300 mg were similar to those in former or never smokers receiving 150 mg in previous studies. Further studies should investigate this erlotinib dose in current smokers (45).

Another phase III randomized trial, the BeTa Lung study, evaluated the combination of erlotinib and bevacizumab versus erlotinib plus placebo in 636 patients with advanced NSCLC who progressed during or after first-line therapy. Median OS was 9.3 months for the bevacizumab plus erlotinib arm and 9.2 months in the erlotinib plus placebo group (HR 0.97). Median PFS was 3.4 months and 1.7 months, respectively (HR 0.62). OR was 12.6\% and 6.2\%, respectively (\( p=0.006 \)). The safety profile was consistent with those known for each drug (46). The study showed no statistically significant difference in OS between the two arms (primary endpoint), with a doubled time of PFS favouring the combination arm. Analysis of subsequent lines of treatment after disease progression showed that most patients in the erlotinib plus placebo arm received post-protocol therapies including bevacizumab-containing regimens. This may explain why the significant PFS benefit observed did not translate into an OS benefit.

A phase IV trial, the TRUST study, employing erlotinib, mainly as second- or third-line treatment, in advanced NSCLC patients was performed worldwide. The results reporting the general practice use of erlotinib were superimposable with those reported by trial BR.21, confirming the drug efficacy and safety in an extended subset of patients closer to clinical practice (47-49).

**Mechanisms of Resistance to Erlotinib**

Unfortunately patients who initially benefited from the erlotinib therapy at a certain point of their illness experienced a progression of their disease. Over time (median of 6-12 months), most of the developed tumours acquired resistance to EGFR-TKIs. The most important mechanisms of resistance to EGFR-TKIs are: activation of EGFR-independent and tumour-induced angiogenesis, activation of alternative TK receptors which bypass the EGFR pathway, independent or constitutive activation of intracellular molecular effectors downstream to EGFR, and EGFR gene mutations or loss of the target. This means that in addition to primary resistance to anti-EGFR therapies, resistance eventually develops in most NSCLC patients who initially respond to gefitinib or erlotinib and in which sensitising EGFR mutations harbour, leading to disease progression during treatment. In these cases, acquired resistance to EGFR inhibitors was shown to be associated with the occurrence of an additional EGFR gene mutation (50, 51). The most studied of such EGFR mutations occurs in exon 20 at position 790 in the kinase domain of the EGFR gene, leading to a substitution of methionine for threonine, which would change the conformation of the receptor and block the binding of gefitinib or erlotinib to the active site, creating resistance to these EGFR-TKIs (51). The secondary T790M mutation occurs in 50\% of patients with mutated EGFR with TKI resistance, and \textit{in vitro}, this mutation negates the hypersensitivity of activating EGFR mutations. Sensitive detection methods have identified a proportion of TKI-naive tumours that carry T790M, and these resistant clones may be selected after exposure to gefitinib or erlotinib. Other secondary resistance mutations (D761Y, L747S, T854A) seem to be rare. It is possible that other kinases, such as insulin-like growth factor-1 receptor (IGF-1R) might also be selected to bypass EGFR pathways in resistant tumours. The growing preclinical data in EGFR-mutated NSCLC with acquired resistance to gefitinib or erlotinib has increased the number of clinical trials testing novel EGFR inhibitors that \textit{in vitro} inhibit T790M (neratinib,_gridelli@et al. Erlotinib in NSCLC (Review)
XL647, BIBW 2992, and PF-00299804), MET, or IGF-1R inhibitors in combination with EGFR TKIs, and heat-shock protein 90 inhibitors (52). As already discussed, KRAS mutations were described to be associated with resistance to EGFR TKIs in NSCLC (44). Ongoing preclinical and clinical research in EGFR-mutated NSCLC has the potential to significantly improve the outcomes of patients with these somatic mutations.

Conclusion

A series of studies are planned to contribute to our understanding of the role of erlotinib in NSCLC treatment. In our opinion, major areas of clinical research are: the assessment of erlotinib in the adjuvant treatment, in combination with chemotherapy and/or radiotherapy in locally advanced disease, in the first-line therapy of advanced disease in patients harbouring activating EGFR mutations, and in combination and/or sequence with cytotoxic treatments and/or other molecular target agents. Another development could be multitargeted inhibition, combining the blockade of angiogenesis, ras/rat/ERK and EGFR. In this context, an interesting multitargeted agent with a low toxicity profile is sorafenib. A phase II, randomized, multicenter clinical trial investigating if the combinations of erlotinib and sorafenib or gemcitabine plus sorafenib could be active and tolerated in elderly or PS 2 NSCLC patients has completed the accrual, and the results are expected in the first part of 2010 (53).

However, the optimization of the therapeutic impact of erlotinib in NSCLC will be more defined when more reliable predictive factors are identified. To date, EGFR gene mutations are associated with a higher possibility of a long lasting therapeutic response and efficacy to erlotinib.

References


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