REVIEW ARTICLE

Targeted therapies in non-small cell lung cancer

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Date accepted for publication 11 August 2008

Abstract
Chemotherapy now has an established role in the treatment of non-small cell lung cancer, with randomised evidence supporting a survival benefit in both advanced disease and the adjuvant setting. The availability of newer cytotoxic agents has not led to further improvement in outcome, and novel approaches are needed. Growth factor-mediated signalling pathways are frequently subverted in human cancers, so that physiological processes become abnormally regulated by oncogene products such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF). Drugs targeting EGFR and VEGF have already demonstrated improved survival compared with standard of care in lung cancer, and the evidence supporting the use of these and related agents is reviewed here. These newer agents are in general cytostatic rather than cytotoxic, so that clinical benefit can be associated with stable disease rather than with disease response alone, and the impact of this on imaging modalities used to assess response in trials and clinical practice is discussed.

Keywords: Non-small cell lung cancer; targeted therapy.

Introduction
The biology of non-small cell lung cancer (NSCLC) continues to be dissected at the molecular level, and this is now allowing the rational development of novel targeted therapeutic approaches, exemplified by a class of small molecules inhibiting the epidermal growth factor receptor (EGFR). The EGFR oncogene, with the related protein HER2, forms a key component of signalling pathways driving many cancers (Fig. 1), and over-expression and mutation have been identified in some cases of NSCLC, especially those of the adenocarcinoma histological subtype.

Most patients with NSCLC present with advanced disease, which is not amenable to radical treatment. For this majority, chemotherapy with a platinum-containing combination of drugs remains the treatment of choice for patients requiring first line treatment, although response rates are modest, and survival benefit measured in months. The availability of several newer cytotoxic drugs over the last 15 years has not led to further improvement in results, and there is a consensus that chemotherapy-based approaches in the treatment of advanced NSCLC have reached a plateau. Second line treatment with docetaxel or pemetrexed has also been shown to palliate symptoms effectively, but third line chemotherapy treatment offers no advantage over best supportive care. Lung cancer research has increasingly been focused on the identification and use of additional novel targeted agents to improve prognosis in this disease, which continues to be a leading cause of cancer mortality.

The current evidence for use of novel therapies in lung cancer is reviewed here. Emphasis is placed on the agents most advanced in their clinical development, namely antagonists of EGFR and vascular endothelial growth factor receptor (VEGFR) signalling pathways.

Targeting EGFR
Classes of agents targeting EGFR include small molecular inhibitors of the intra-cellular tyrosine kinase domain, and monoclonal antibodies. The small molecules are
Despite the promising response rates in the phase II studies in the second line setting, superior overall survival for gefitinib in a large negative phase III study (ISEL) did not reach significance. This study compared best supportive care plus gefitinib or placebo, with a significantly superior response rate of 8% versus 1% ($p < 0.0001$) in favour of gefitinib, but no significant difference in overall survival (median survival 5.1 months versus 5.6 months with 1-year survival 27% versus 21%). Again this trial had a pre-planned subgroup analysis showing improved survival in never smokers and patients of Asian origin.6,7

The acceptable toxicity profile of these agents in comparison with cytotoxiccs is a major feature favouring their use in this patient group. The positive clinical outcomes following both erlotinib and gefitinib compare favourably with second line chemotherapy response rates of 7% for docetaxel21 and highlight the potential role for these drugs especially in those unlikely to tolerate the toxicities of chemotherapy. Indeed the results of a randomised comparison of second line gefitinib versus docetaxel (INTEREST) have recently been presented in abstract form and show equivalent survival in the targeted therapy arm. Median survival was equivalent, with a trend towards increased quality of life measured by FACT-L (25.1% for gefitinib compared to 14.7%)8. Erlotinib is also under evaluation in this setting in the TITAN trial, with EGFR analysis prior to randomisation.

Dramatic and sustained clinical benefit is well recognised with both erlotinib and gefitinib in a small subset of patients. The modest improvement in median survival seen with erlotinib, and non-significant survival difference with gefitinib, in the phase III studies compared to best supportive care, highlights the need for predicting with more accuracy which patients that may benefit in terms of overall survival.

Recent studies have focused on predicting, using demographic or molecular markers, which patients will benefit, and whether efficacy is improved in combination with chemotherapy or other targeted agents. The presence of kinase domain EGFR mutations was initially described in patients responding to gefitinib and erlotinib9-11 and is now recognised as an important predictor of response, albeit without sufficient sensitivity or specificity to be used alone as a selection criterion for second line treatment. EGFR mutations are somatic and occur in tumours in 10-15% of western populations, compared with 30-40% of east Asians12. However, mutation status has been studied in particular as a predictive marker in the first line use of EGFR inhibitors. Non-randomised studies show encouraging results with response rates ranging from 55 to 82%13-18. There are prospective randomised trials ongoing of selection using mutation analysis, including studies conducted by the Spanish Lung Cancer Group and in several groups in Asia. Other methods of analysis include fluorescence in situ hybridisation for EGFR amplification and high polysomy, and protein expression using immunohistochemistry.

Reversible EGFR inhibitors

Erlotinib and gefitinib are orally bioavailable reversible tyrosine kinase inhibitors, which selectively inhibit the intracellular catalytically active domain of EGFR. The single agent use of the reversible EGFR inhibitors in the second or third line setting has shown clinical benefit. BR21 a multi-centre Canadian phase III study looked at erlotinib in a randomised comparison with placebo, response rates were 8.9%; median survival 6.7 vs 4.7 months, hazard ratio 0.73, $p < 0.001$, in particular in non-smoking, east Asian, female and adenocarcinoma subgroups44. A quality of life evaluation in this trial showed significantly longer time to symptom deterioration in the erlotinib arm for cough, dyspnoea and pain, with associated improvement in physical function and global quality of life.

Gefitinib showed similar response rates (9-19%, median overall survival 13.6 months in patients with improvement of symptoms at dose of 250 mg once a day) in previously treated patients in two large phase II trials (IDEAL 1 and 2)5,6, 40% of patients demonstrated symptomatic improvement. The main side effects with these drugs, i.e. diarrhoea and rash, are readily controllable in most patients.

Figure 1 EGFR biology. The epidermal growth factor receptor (EGFR) forms a dimer with the related receptor HER2 in response to binding of growth factor ligand. This causes activation of the intracellular tyrosine kinase domains, and in turn activation of downstream signalling pathways that result in cell proliferation and survival. In some cases of NSCLC this physiological signalling process is subverted by activating mutations of either EGFR or HER2, or overexpression of these gene products.
Additional molecular events in NSCLC that are thought to be important include activating mutation of K-Ras, which confers resistance to EGFR inhibition, and therefore may be of use in negative selection (identification of patients who will not benefit from EGFR inhibition).

Despite activity as single agents in second and third line use, neither erlotinib nor gefitinib used in combination with chemotherapy have yet demonstrated any improvement in outcome compared with chemotherapy alone. The addition of erlotinib to chemotherapy (platinum doublet) in the first line setting has so far not shown any statistical difference in survival\textsuperscript{[19,20]}. This is mirrored in the gefitinib trials INTACT1 and INTACT2\textsuperscript{[21,22]}. These studies were conducted in unselected patient groups, but given the results of the BR21 subgroup analysis, a key area of interest is in groups of patients predicted clinically to have higher response rates such as never/light smokers with adenocarcinoma histology. The Cancer and Leukaemia Group B 30406 phase II trial within this mutation-positive group is comparing first line erlotinib with or without carboplatin/paclitaxel.

The advantages in principle of these agents in comparison to chemotherapeutics include a decrease in most toxicities, except rash and diarrhoea. Their use is therefore an attractive option in patients with a poor performance status due to disease, multiple comorbidities or older age group. Patients who are deemed not fit for chemotherapy, by virtue of poor performance status or impaired renal function, may be randomised in the first line setting to treatment with erlotinib or placebo in the phase III clinical trial TOPICAL. The rationale for this trial is provided by phase II data on the use of erlotinib as first line treatment in unselected patients over the age of 70 showing a response rate of 10% and a median overall survival 10.9 months\textsuperscript{[23]}. However these results are in contrast with a phase II direct comparison of erlotinib versus chemotherapy (carboplatin/paclitaxel) in the first line setting in patients with performance status 2 showing a trend towards superior progression-free survival in the chemotherapy arm and response rates of 2. These data, so far presented only in abstract form, show a response rate of only 2% in the erlotinib arm, and median overall survival of 6.6 versus 9.6 months in favour of the chemotherapy arm. Patients were stratified by age and stage but not on a molecular basis\textsuperscript{[24]}. A phase II randomised trial of gefitinib versus vinorelbine in 196 untreated elderly patients (INVITE) showed non-significant results again in favour of the chemotherapy arm (hazard ratio 1.19, \(p = 0.31\)). Toxicity analysis as expected showed more grade 3/4 events in the vinorelbine arm (55% vs 41%), but interestingly overall survival in EGFR FISH positive patients revealed a hazard ratio of 3 in favour of the vinorelbine arm, which was again the opposite to that expected\textsuperscript{[25]}.

Other settings for EGFR inhibitor use being studied include adjuvant and locally advanced disease, and maintenance indications. Gefitinib did not improve survival when added following chemoradiation, and in fact median survival in the experimental arm was inferior to that for patients receiving placebo\textsuperscript{[26]}.

The use of EGFR-targeted small molecules seems likely to be guided in the future by some combination of molecular biomarkers, likely to include EGFR mutation status and/or EGFR FISH for example. However, at present no algorithm is yet available, and where erlotinib is not universally available, demographic features such as never-smoking status are useful in patient selection.

### Irreversible inhibitors

Second generation agents are in development, which in contrast to gefitinib and erlotinib, are irreversible inhibitors of EGFR. As they also have specificity for the HER2 kinase they are termed dual kinase inhibitors. The agents under investigation at present include BIBW2992 and HKI-272. These drugs have shown a comparable side effect profile to other EGFR inhibitors including diarrhoea, rash, fatigue and mild epistaxis in phase I studies, and promising clinical efficacy with partial responses seen in 3 of 12 NSCLC patients treated in a phase I trial of BIBW2992, and stable disease at 12 weeks in 5 of 12 patients with NSCLC in a phase I trial of HKI-272 following progression after a reversible EGFR inhibitor. Phase II and III trials of these agents are ongoing.

Resistance to first generation reversible EGFR inhibitors invariably occurs in all responding patients after a variable time on treatment. Several studies have isolated EGFR T790 mutations in tumour cells from patients who have relapsed on EGFR inhibitors\textsuperscript{[27,28]}. Molecular understanding of this resistance mechanism suggests that second generation inhibitors may be potentially effective treatments in this situation.

### Monoclonal antibodies

Despite low response rates as single agents\textsuperscript{[29]}, monoclonal antibodies specific for EGFR such as cetuximab demonstrated moderate anti-tumour activity in randomised phase II studies in combination with platinum-based chemotherapy\textsuperscript{[30,31]}. Cetuximab is a chimeric monoclonal antibody against the extracellular domain of EGFR, licensed for use in colorectal and in head and neck cancers. The addition of cetuximab to first

### Table 1 Phase II trials of EGFR inhibitors in patients selected for EGFR mutation

| Patients screened | EGFR mutations | Agent | Response rate (%) |
|------------------|----------------|-------|-------------------|
| Inoue            | 99             | 16    | Gefitinib         | 75 |
| Paz-Ares         | 1047           | 127   | Erlotinib         | 82 |
| Okamoto          | 118            | 32    | Gefitinib         | 75 |
| Sutani           | 100            | 38    | Gefitinib         | 78 |
| Morikawa         | 123            | 46    | Gefitinib         | 62 |
| Sequist          | 98             | 31    | Gefitinib         | 55 |
line chemotherapy in a recently presented phase III randomised trial, in 696 patients with advanced disease, showed equivalent progression-free survival (4.2 versus 4.4 months) according to independent radiology review[32]. A further randomised phase III study (FLEX) has been completed but no results yet presented.

Once again patient selection in the use of cetuximab in NSCLC is problematic; in colorectal cancer there appears to be no correlation between EGFR expression and outcome. It has been noted that there is synergy when cetuximab is used in conjunction with radiotherapy in treatment of head and neck cancer, and this is under evaluation in NSCLC.

Panitumumab, another monoclonal antibody specific for EGFR, has also been studied in NSCLC. No responses were seen in 14 patients in a phase I clinical trial, and in a randomised phase II trial in combination with carboplatin and paclitaxel in 166 untreated patients there was no additional benefit in response rate, time to progression or median survival seen in the panitumumab arm. Matuzumab in combination with paclitaxel in advanced NSCLC showed objective responses in 23% patients in a phase I setting. Phase II trial data is awaited as second line therapy in combination with pemetrexed.

**Monoclonal antibody against HER2**

EGFR signals most efficiently upon heterodimerisation with the related receptor tyrosine kinase HER2 (Fig. 1). Thus HER2 is an attractive target in NSCLC. However, the HER2 specific monoclonal antibody trastuzumab in combination with cytotoxic drugs has shown little additional efficacy as first line therapy in this disease[33] although these results were hampered by the inclusion of patients with tumours who did not stain strongly for HER2 protein. HER2 over expression occurs in only approximately 10% of patients with NSCLC, and activating mutations have been detected in approximately 4% of adenocarcinomas[34]. It is therefore thought that any potential role for HER2 antibodies may lie in combination with other targeted agents. HER2 status may prove important in the prediction of response to EGFR-targeted agents in view of the dimerisation between EGFR and HER2 receptors.

**Targeting VEGF**

Agents that target the vascular endothelial growth factor pathway inhibit tumour angiogenesis. They include the anti-VEGF monoclonal antibody bevacizumab and the soluble VEGF receptor aflibercept, as well as intracellular small molecule VEGF inhibitors such as AZD2171, sorafenib, sunitinib and vandetanib (Fig. 2).

Bevacizumab has shown activity in two phase III studies, ECOG 4599 and AVAIL, in the chemo-naive, locally advanced or metastatic setting. ECOG 4599 studied carboplatin/paclitaxel with or without bevacizumab, at a dose of 15 mg/kg, with an overall median survival benefit of 2 months (10.2 versus 12.5 months, hazard ratio 0.77, \( p = 0.007 \)) and a 2-year survival improved from 15 to 23%, improved progression-free survival from 5.4 to 6.2 months and response rates from 15% for chemotherapy alone to 35%[35]. AVAIL was not powered for overall survival, but progression-free survival data have recently been presented for the two arms comparing gemcitabine/cisplatin with or without bevacizumab. PFS was superior in both 7.5 mg/kg and 15 mg/kg bevacizumab arms with a hazard ratio 0.75 and 0.82, respectively[36]. Both of these trials used maintenance bevacizumab, the necessity of which remains to be clarified. The lower 7.5 mg/kg dose of bevacizumab did not show inferiority and is therefore the dose of choice for further trials. The exclusion criteria for these randomised controlled studies included squamous cell histology, brain metastases and existing uncontrolled hypertension due to toxicities of hypertension and pulmonary and intra-cranial haemorrhage noted in phase I and II studies[37]. Despite these exclusions, in the ECOG 4599 there was still a significant increase in the number of treatment-related deaths, 2 on the chemotherapy alone arm versus 15 on the bevacizumab arm. Of these deaths, five were due to pulmonary haemorrhage, five due to neutropenic sepsis, two cerebrovascular accidents, two gastro-intestinal bleeds and one pulmonary embolism.

The combination of bevacizumab with an EGFR inhibitor such as erlotinib is also an area of interest and there have been several phase I/II studies. Response rates in previously treated patients with NSCLC were 20% with a progression-free survival of 6.2 months and overall survival of 12.6 months[38]. Given the paucity of data.
supporting a major survival benefit, and the significant proportion of patients ineligible for treatment because of histological subtype or co-morbidity, bevacizumab has not yet become a universal standard of care in the first line setting.

There are no currently available molecular predictive markers for response, and plasma VEGF levels were not shown to correlate with outcome in the ECOG 4599 trial. The use of monoclonal anti-VEGF antibodies in the adjuvant setting, in squamous histology, and in patients with treated brain metastases is under investigation.

VEGF is the ligand for a group of three receptors, VEGFR-1, 2 and 3 (also known as Flt-1, KDR and Flt-4, respectively). Small molecular inhibitors of this receptor kinase family are in development. These so-called multi-targeted inhibitors include vandetanib (ZD6474), which inhibits EGFR and VEGFR-2, as well as sorafenib, sunitinib and AZD2171, which have broad specificity for receptor tyrosine kinases including members of the VEGFR family. Vandetanib has been combined with gefitinib and with docetaxel in second line phase II studies including squamous cell histology. Vandetanib plus docetaxel prolonged progression-free survival compared with docetaxel alone\[39\], as did vandetanib compared with gefitinib. AZD2171 is administered orally and targets VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, c-Kit. It has activity in NSCLC, and phase II studies so far have shown response rates in combination with carboplatin and paclitaxel; phase III trials both in combination with chemotherapy are ongoing in patients with NSCLC.

Sunitinib and sorafenib are both approved for use in advanced renal cell cancer and are undergoing evaluation in phase II and III trials in NSCLC. Aflibercept is an engineered soluble receptor from extracellular domains of VEGFR-1 and -2. It binds to all isoforms of VEGF and has a higher affinity than bevacizumab for VEGF A and B. The toxicities in early phase I trials were similar to other anti-VEGF agents, and the drug is currently entering phase III development.

**Conclusion**

New targeted therapies are beginning to have a significant impact on the outcome in lung cancer. Two such agents have so far demonstrated median survival benefits in randomised controlled trials\[4,35\], and other related drugs are in late stages of clinical development. Many other classes of novel therapy are also in clinical trials in NSCLC, including kinase inhibitors interacting with other signalling pathways, antisense approaches and vaccines.

Despite the advances made to date, the median survival improvements in unselected patients with advanced disease treated with the EGFR inhibitor erlotinib, or with the anti-VEGF antibody bevacizumab, have been modest. However clinicians have long recognised that dramatic and sustained responses occur in some patients treated with EGFR inhibitors. At last in the case of erlotinib, it is becoming clear that the subset of patients more likely to benefit includes those with tumours harbouring EGFR mutation. To date there are no biomarkers available for selection of patients for anti-angiogenic therapies. The understanding of the molecular signatures predicting response will be a key step in the development of these and other novel agents, both in advanced disease, and increasingly in the adjuvant setting. It is in the treatment of NSCLC patients following potentially curative surgery that the new agents may eventually have the most dramatic impact on survival by significantly increasing the proportion cured, rather as the HER2 antibody trastuzumab has transformed the adjuvant treatment of HER2-expressing breast cancer\[40]\.

Many of the newer agents reaching the clinic in this and other solid tumours are cytostatic rather than cytotoxic in their activity. This has implications for the use of imaging in assessing the efficacy of these drugs when used as single agents, both in the individual patient, and for the purposes of evaluation of efficacy in clinical trials. Stable disease is recognised as a significant endpoint in the evaluation of clinical benefit associated with many targeted agents, and a focus on only conventional complete or partial responses assessed in the conventional manner using RECIST\[41\] may underestimate efficacy and risk discontinuation of the development of active new agents\[42\]. In part to address this issue, functional imaging is increasingly used to assess clinical response, and especially to provide information on the development of new therapies\[43\].

The development of imaging biomarkers within this field is likely to prove an invaluable tool in accurate staging and monitoring, with prognostic significance, and therefore is becoming invaluable within drug development. Functional imaging such as dynamic contrast enhanced computed tomography (CT), dynamic magnetic resonance imaging (MRI) and fluorodeoxyglucose (FDG)-positron emission tomography (PET) have been studied to a limited extent so far in assessing response to chemotherapy. FDG-PET is used as a tool for response assessment and has been studied in various tumours treated with chemotherapy especially within lymphoma, however, to date there are almost no data for targeted therapies. These techniques are likely to become increasingly important in the future\[44,45\].

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