EVOLUTION OF BIOLOGICAL THERAPIES IN NON-SMALL CELL LUNG CANCER

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Abstract

This article explores recent clinical developments of biological or targeted therapies in non-small cell lung cancer. Molecular research has given us a greater understanding of tumour biology and has led to identification of targets for therapy. A key pathway involves the epidermal growth factor receptor. Inhibitors of the tyrosine kinase domain (erlotinib, gefitinib) have had a clear impact in the treatment of advanced non-small cell lung cancer and a monoclonal antibody against epidermal growth factor receptor (cetuximab) also appears to have benefit. Inhibiting angiogenesis (or tumour blood supply growth) appears a promising approach with small but real gains being made with bevacizumab (a monoclonal antibody targeting the vascular endothelial growth factor receptor). Other new molecules targeting angiogenesis, apoptosis and intracellular growth pathways are being tested.

Until the late 1990s, it had not been clear that any effective systemic therapy existed in non-small cell lung cancer (NSCLC), although there was a suggestion of benefit with cisplatin in an earlier meta-analysis. Multiple studies have since demonstrated a survival and quality of life advantage with chemotherapy.

Nevertheless, the notion of targeted therapies has promised improved efficacy and reduced toxicity through greater selectivity of cancer cell processes. In this review, the development of these novel agents is discussed, with emphasis on the epidermal growth factor receptor (EGFR) pathway and angiogenesis.

Epidermal growth factor receptor inhibitors

The EGFR family has been known for over a decade as a potential therapeutic target. The receptors are implicated in cancer progression through effects on cell-cycle stimulation, apoptosis, angiogenesis and metastasis. Epidermal growth factor receptor over-expression has been shown to be an adverse prognostic factor in NSCLC.

The initial promise was seen with the development of inhibitors of the tyrosine kinase (TKI) domain of EGFR. Gefitinib was initially tested in the Phase I setting after promising pre-clinical data showing inhibition of receptor auto phosphorylation and xenograft growth. Doses up to 1000mg were used with the limiting toxicities of rash and diarrhea.[1] The rash management has since become incorporated in lung cancer care, occurring primarily because of the abundant EGFR expression in keratinocytes and sebaceous glands. Interestingly, there appears to be a relationship between rash development and the probability of clinical benefit.[2]

The Iressa Dose Evaluation in Lung Cancer 1 and 2 studies compared 250 and 500mg doses in patients who had progressed on prior chemotherapy. No clear benefit was seen with the higher dose and this led to the incorporation of the 250mg dose in Phase III studies.[3,4]

Meanwhile, erlotinib, a sister molecule with a similar action, was pushed rapidly into Phase III development at 150mg daily. Both agents were combined with concurrent chemotherapy in the TALENT/TRIBUTE studies (erlotinib) and INTACT1/2 (gefitinib). Disappointingly, all studies showed no advantage for the combination.[5-7] It has been questioned whether the addition of an EGFR inhibitor induces cell cycle arrest. A similar effect has been seen in breast cancer when chemotherapy was administered concurrently with the hormonal therapy tamoxifen (which is a known cytostatic agent).

A parallel set of studies however, compared the TKIs with best supportive care (placebo). The BR21 study was a landmark study showing a survival advantage with the use of erlotinib, the first biological or targeted agent to do so in NSCLC. The median survival was 6.7 months and one-year survival 31% with erlotinib, compared with 4.7 months and 22% for placebo.[8]

Interestingly, the Iressa Survival Evaluation in Lung Cancer (ISEL) study comparing gefitinib with placebo only identified an impact on time to treatment failure (three months versus 2.6 months) but no impact on overall survival.[9] The comparative results have questioned the difference in efficacy of the two drugs. It has however, been argued that the population tested in ISEL were refractory to chemotherapy. Another study investigating consolidation gefitinib following chemo-radiotherapy was closed early because the TKI was not adding efficacy (and arguably looked inferior to standard therapy).[10] Somewhat reassuringly, a more recent study comparing gefitinib with docetaxel (the standard of care in second-line treatment in NSCLC) showed equivalent survival, confirming its activity in advanced lung cancer.[11]

Although the agents have shown an overall benefit in NSCLC, it has been apparent from their use that certain patients are more likely to benefit. Clinically, the phenotypes that derive the most benefit are non-smokers, patients with adenocarcinoma, women and Asian patients.[8,12] Assessment of EGFR status has

yielded mixed results. Initial Phase II results, particularly with gefitinib, have not demonstrated EGFR expression (assessed by immunohistochemistry) as a useful predictive marker of benefit. In BR21, immunohistochemistry was significantly predictive of a survival advantage by univariate, but not multivariate analysis. A similar signal was seen for EGFR gene copy analysis through fluorescent in-situ hybridisation. Interestingly, it was decided to use these tests as inclusion criteria in the current adjuvant erlotinib study despite the lack of conclusive evidence.

Unusually impressive responses have been noted in patients with tumours carrying an activated form of the EGFR receptor.[13,14] Mutation analysis of BR21 patient tumours however, has not demonstrated any relationship with survival.[12]

In conclusion, the average patient stands to gain from these therapies, but no particular factors beyond the clinical profile truly assist in treatment decisions, particularly in the cost rationalisation of treatment in NSCLC.

The EGFR pathway can also be blocked with the use of monoclonal antibodies directed against the external domain of the receptor. There are multiple mechanisms of action including blockade of signal transduction, promotion of receptor internalisation and degradation, and antibody-dependent cellular toxicity. Cetuximab is a humanised antibody that has previously demonstrated efficacy in colorectal cancer. It has also recently been assessed in EGFR positive NSCLC. The FLEX (First Line in lung cancer ErbituX) study presented at the American Society of Clinical Oncology showed that the addition of cetuximab to chemotherapy improved median survival from 10.1 months to 11.3 months, with particular benefits seen in caucasians and patients with adenocarcinoma. The toxicities seen are typical of EGFR blockade, namely rash and diarrhoea.[15]

Anti-angiogenic targeted therapy

One of the other key areas of targeted anti-cancer drug development is the area of anti-angiogenesis. The reliance of tumours on the development of new blood vessels (angiogenesis) in order to grow is now an established concept in tumour biology. Furthermore, it is known that angiogenesis in tumours can be switched on, usually by over-expression of pro-angiogenic factors, and that blocking these factors can inhibit tumour growth and metastasis.[16] However, this process is complex and involves interaction with the host micro-environment and extracellular matrix, where vascular sprouting must traverse and many growth factors can reside. In lung cancer, there are a number of studies that have demonstrated that high micro vessel density or over-expression of angiogenic growth factors is associated with a poor prognosis in terms of metastasis development and survival.[17]

A number of angiogenesis inhibitors have been developed and explored in lung cancer. These can be classified into direct inhibitors which target key angiogenic processes (eg. matrix metalloproteinase inhibitors (MMPIs) affecting extracellular matrix protein degradation), or indirect inhibitors targeting key mediators of angiogenesis eg. angiogenic growth factors such as vascular endothelial growth factor (VEGF) or its receptor(s), and platelet derived growth factor among others.[18]

The first generation of clinical trials of angiogenesis inhibitors in lung cancer involved the addition of an MMPI to chemotherapy. Unfortunately several Phase III trials evaluating the addition of an MMPI to first-line standard chemotherapy compared with chemotherapy/placebo failed to demonstrate any advantage, in both NSCLC and small cell lung cancer.[19,20] And these drugs were found to be associated with musculoskeletal toxicity.

The only successful clinical trials of angiogenesis inhibitors have focused on VEGF as the main target. Bevacizumab (Avastin®), a humanised monoclonal antibody, demonstrated tumour growth inhibition and synergy with chemotherapy in pre-clinical models and has demonstrated synergy with chemotherapy in metastatic colorectal cancer, where it is Therapeutic Goods Administration registered.[21] In NSCLC, a pivotal randomised Phase II clinical trial was reported in 2004. Here, 99 patients were randomly assigned to bevacizumab 7.5 or 15mg/kg plus carboplatin and paclitaxel Q 3 weekly or carboplatin paclitaxel alone (n = 32).[22] Compared with control (carboplatin paclitaxel alone), treatment with carboplatin paclitaxel and bevacizumab (15mg/kg) resulted in a higher response rate, longer median time to progression and a modest increase in survival. Bleeding was the most prominent adverse event with minor epistaxis most common (44%), but major haemoptysis was seen in six patients, four of which were fatal. The major haemoptysis was found to be associated with squamous cell cancer histology, tumour necrosis and cavitation and disease location close to major blood vessels.[22] Other unique bevacizumab related toxicity seen was hypertension and asymptomatic proteinuria.

This trial led to a landmark US Phase III clinical trial (ECOG 4599) of first–line paclitaxel carboplatin alone or with bevacizumab in SIIIB/IV NSCLC (n = 878). This trial excluded patients with squamous cell cancer, brain metastases or clinically significant haemoptysis. The primary endpoint was overall survival. Median survival was 12.3 months (paclitaxel carboplatin + bevacizumab arm) compared with 10.3 months (paclitaxel carboplatin alone (Hazard Ratio (HR) 0.79; P=0.003)).[23] The median progression-free survival in the two arms was 6.2 and 4.5 months, respectively (HR 0.66; P<0.001), with corresponding tumour Response Rate (RR) of 35% and 15% (P<0.001). Clinically significant bleeding was seen in 4.4% and 0.7%, respectively (P<0.001). There were 15 treatment related deaths in the paclitaxel carboplatin + bevacizumab arm, including five from pulmonary haemorrhage.

Supporting the results from this study were the findings from a second randomised Phase III study (N = 1043) comparing two doses of bevacizumab plus cisplatin/gemcitabine (CG) versus cisplatin/gemcitabine plus placebo in first line non-squamous cell cancer SIIIB/IV NSCLC, presented in abstract form in 2007.[24] Progression free survival was the primary endpoint and both doses of bevacizumab significantly improved progression free survival (7.5 mg/kg: HR 0.75, P=0.002); 15 mg/kg HR 0.82, P=0.03) and RR (34 and 30%

respectively for bevacizumab arms compared with 20% for CG). Grade III/IV hypertension was seen in < 9% of bevacizumab patients, with GIII/IV haemoptysis in < 1.5%. The safety of bevacizumab is currently under evaluation in an international observational study. Preliminary results in > 1000 NSCLC patients have confirmed the existing well described safety profile without central nervous system haemorrhage.[25]

The other broad class of angiogenesis inhibitors under evaluation are the small molecule receptor TKIs. Several, targeting more than one angiogenesis promoting TK receptor, are in clinical development.[11] Preliminary results from Phase II trials have shown promise for the multi-kinase inhibitors ZD6474, sunitinib and sorafenib amongst others.[26-28] Further Phase II and Phase III trials evaluating anti-angiogenic TKIs are underway and final results are awaited.

Finally, the Phase III efficacy results with bevacizumab and the promising Phase II results from several oral anti-angiogenic TKIs have confirmed the important role that angiogenesis inhibitors may come to have in the future management of lung cancer. It is important to note that patient selection has and will be important in the future use of these agents. Furthermore, the use of angiogenesis inhibitors has identified several broad 'class' side-effects such as hypertension, bleeding and proteinuria, indicating that careful patient monitoring will also be required.

New approaches

A huge array of novel agents is currently under investigation. Another receptor that shows promise as a therapeutic target is the insulin-like growth factor receptor 1 (IGFR1). This transmembrane protein is implicated in oncogenic transformation, cancer cell growth and survival. Molecules such as monoclonal antibodies against IGFR1 are being tested in early phase studies in NSCLC.[29] Downstream cellular kinases such as PI3 Kinase also appear attractive targets for novel therapeutics.

Much of the approach until recently has been directed towards inhibiting uncontrolled growth. The stimulation of apoptosis (programmed cell death) is a different angle of attack. Agonists of so-called 'death receptors', such as the tumour necrosis (TNF) related apoptosis-inducing ligand (TRAIL) receptor family, may promote apoptosis of cancer cells.[30] Downstream manipulation of the caspase pathway may also trigger apoptosis and this is being investigated.

Conclusion

Management of NSCLC is entering a new era, with greater understanding of molecular biology and the resultant development of targeted therapies. Better understanding of factors predicting benefit is needed however, as the cost of these therapies is becoming prohibitive for many individuals and societies. These agents must then be tested in populations enriched by patients bearing these predictive factors and particularly in the early stage lung cancer patients where the chance of cure is more realistic. The mechanism of cancer growth is complex and it is also likely that multiple therapies will be required in concert to achieve a meaningful impact on lung cancer in the future.

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