Molecular Target Therapy of Lung Cancer

A new horizon of targeted therapy in management of lung cancer

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1 Introduction

Cisplatin-based combination chemotherapy using one of the novel cytotoxic agents, such as gemcitabine or taxane, prolongs survival of patients with advanced non-small cell lung cancer (NSCLC). The recent published phase III study that compared paclitaxel/cisplatin to gemcitabine/cisplatin, docetaxel/cisplatin or paclitaxel/carboplatin has shown equal efficacy with the exception of longer progression-free survival from the gemcitabine/cisplatin combination[1]. Overall tumor response rates of 1,155 eligible patients was 19% with median survival of 7.9 months only. Findings from other major randomized comparative studies were similar. Table 1 summarized the tumor response rate and survival of these studies[1-4]. Hundreds of patients received platinum-based new drug doublets and the overall response rate was persistently reported at only about 20% to 30%. Survivals were better than the first generation of combination chemotherapy but the best median survival was less than 10 months and 1-year survival rate was persistently less than 45%.

Tab 1  Efficacy of platinum-based new drug doublets

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>n</th>
<th>Response rate</th>
<th>Median survival</th>
<th>1-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly</td>
<td>Tax/CBDCA</td>
<td>208</td>
<td>25%</td>
<td>8 months</td>
<td>38%</td>
</tr>
<tr>
<td>(SWOG 9509)</td>
<td>VNB/DDP</td>
<td>202</td>
<td>28%</td>
<td>8 months</td>
<td>36%</td>
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<tr>
<td>Schiller</td>
<td>Tax/DDP</td>
<td>292</td>
<td>21%</td>
<td>8.1 months</td>
<td>31%</td>
</tr>
<tr>
<td>(ECOG 1594)</td>
<td>GEM/DDP</td>
<td>288</td>
<td>21%</td>
<td>8.1 months</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>Docet/DDP</td>
<td>293</td>
<td>17%</td>
<td>7.4 months</td>
<td>31%</td>
</tr>
<tr>
<td>Scagliotti</td>
<td>Tax/CBDCA</td>
<td>290</td>
<td>15%</td>
<td>8.3 months</td>
<td>35%</td>
</tr>
<tr>
<td>(ILCP)</td>
<td>GEM/DDP</td>
<td>205</td>
<td>30%</td>
<td>9.8 months</td>
<td>37%</td>
</tr>
<tr>
<td>Smit</td>
<td>Tax/DDP</td>
<td>201</td>
<td>32%</td>
<td>9.9 months</td>
<td>43%</td>
</tr>
<tr>
<td>(EORTC)</td>
<td>VNB/DDP</td>
<td>201</td>
<td>30%</td>
<td>9.5 months</td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td>GEM/Tax</td>
<td></td>
<td>31%</td>
<td>8.1 months</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>GEM/Tax</td>
<td></td>
<td>36%</td>
<td>8.8 months</td>
<td>32%</td>
</tr>
</tbody>
</table>

New innovative approaches are warranted. Cytotoxic chemotherapy is commonly limited by toxicity, and therefore the duration of therapy is restricted to an average of 4 to 6 cycles. Molecular targeted therapy holds the promise to stop cancer growth with less harm to the host. They are supposed to target only the cancer cells and spare the normal tissues. Currently, the major groups of molecular targets that are under intensive investigation include epidermal growth factor receptor (EGFR) inhibitor, angiogenesis inhibitors, antisense oligonucleotides, proteasome inhibitor and cyclooxygenase-2 (COX-2) inhibitor. While a number of other biological pathways are also being investigated, the current available laboratory and clinical data on these five major groups are most mature and promising. Molecular targeted therapies are on the horizon to become the new...
standard treatment for lung cancer.

2 EGFR inhibitor

EGFR is a commonly expressed transmembrane glycoprotein that is a member of the tyrosine kinase growth factor receptor family. About 70% of all cancers express the EGFR but a smaller portion will have overexpression of the receptors\(^5\,6\). The frequency of EGFR expression in NSCLC ranges from 40% to 90%. Upon ligand binding, the tyrosine kinase-dependent intracellular domain of EGFR is activated, thereby triggering cellular mechanisms that regulate cell growth. The downstream signaling networks are extensive and complex and the key pathways include the Raf-Ras-Mek-Erk for proliferation, cell survival and angiogenesis\(^7\). The blocking of tyrosine kinase activity of the EGFR may inhibit these activities leading to cessation of cell growth.

Iressa (gefitinib) is a novel selective EGFR tyrosine kinase inhibitor. The drug blocks the signal transduction pathway for cell proliferation and attains a cytostatic effect. It inhibits both the Akt and MAPK pathways and therefore causes G1 arrest\(^8\). A xenografts model in athymic nude mouse showed that a simple oral dosing could cause marked reduction of tumor size\(^9\). The absolute bioavailability of 60% allows oral dosing at once a day\(^10\). CYP3A4 inhibitor, such as itraconazole, can significantly increase the area under curve (AUC), while CYP3A4 inducer, such as rifampicin, can reduce the AUC. The major route of excretion is via the bile. Iressa is extensively metabolized to a number of components but most are considered to be inactive.

Seven phase I trials involving 328 cancer patients were completed\(^11\,12\). Dose limiting toxicity was diarrhea at 1 000 mg daily. Dose interruption was frequent at 600 mg daily because of skin and diarrheal toxicities. Recommended dosage for phase II/III study was 250 mg and 500 mg daily. In the two trials that included five major recurrent solid tumors there were 9 patients with NSCLC attaining partial response. These studies have laid the foundation of the Iressa Dose Evaluation in Lung Cancer (IDEAL) phase II trials (Table 2). The objectives of these two large randomized double-blind phase II studies were to evaluate Iressa as monotherapy at doses of 250 mg or 500 mg daily for lung cancer patients with prior chemotherapy. Fukuoka et al\(^13\) (IDEAL 1) studied patients with one prior chemotherapy and reported response rate of 18.4% and 19.0% for 250 mg and 500 mg, respectively. Over 30% of patients had stable disease. Median overall survival was 7.6 and 8.0 months respectively. The study confirmed meaningful clinical anti-tumor effect in patients with previously treated NSCLC. Kris et al\(^14\) (IDEAL 2) studied NSCLC patients with 2 or more prior therapy. Of the 216 evaluable patients partial response occurred in 12% and 9% for 250 mg and 500 mg, respectively. However, 43% of patients reported significant improvements in symptoms. There was no significant difference in one year survival and median survival between the two doses. Incidences of diarrhea and acne-like rash were more common with the higher dosage. However, the multinational multicenter randomized study that compares Iressa to second line chemotherapy is ongoing. Target accrual is 1 015 patients and China will contribute 100 patients to this study. The survival outcome of this study will be available in 2006.

Two randomized phase III trials studied the role of Iressa in combination with systemic chemotherapy as first line therapy for patients with advanced NSCLC (Table 2). The Iressa NSCLC Trial Assessing Combination Treatment (INTACT 1) study compared systemic chemotherapy of gemcitabine and cisplatin plus Iressa at two dose levels to placebo\(^15\). A total of 1 093 patients were enrolled and randomized to three arms. The median survival for the two treatment groups with Iressa was 9.9 months and the placebo group was 10.9 months. The one year survival rate was 43% and 41% for 500 mg group and 250 mg group, respectively. The median time to progression was 5.5 months, 5.8 months and 6.0 months for 250 mg group, 500 mg group and placebo, respectively. INTACT 2 is a similar study using paclitaxel and carboplatin plus Iressa or placebo\(^16\). Of the 1 037 enrolled patients, the median overall survival for 250 mg, 500 mg and placebo was 8.7, 9.8 and 9.9 months, respectively. The time to progression was also similar (4.6, 5.3 and 5.0 months, respectively). Conclusions from these two major studies.
have clearly indicated that non-selective use of Iressa added no benefit to standard first line chemotherapy. However, the studies were criticized for failure to document the EGFR status prior to randomization. Only about one third of enrolled patients have available samples for EGFR evaluation. The efficacy of the drug may be diluted by the non-expressors.

<table>
<thead>
<tr>
<th>Study</th>
<th>Subject</th>
<th>n</th>
<th>Response rate</th>
<th>Median survival</th>
<th>1-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDEAL 1</td>
<td>250 mg 2nd or 3rd line therapy</td>
<td>103</td>
<td>18.4%</td>
<td>7.6 months</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>500 mg line therapy</td>
<td>105</td>
<td>19.0%</td>
<td>8.0 months</td>
<td>29%</td>
</tr>
<tr>
<td>IDEAL 2</td>
<td>250 mg 3rd line therapy</td>
<td>102</td>
<td>12%</td>
<td>7 months</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>500 mg therapy</td>
<td>114</td>
<td>9%</td>
<td>6 months</td>
<td>24%</td>
</tr>
<tr>
<td>INT ACT 1</td>
<td>250 mg 1st line with gemcitabine</td>
<td>365</td>
<td>50.3%</td>
<td>9.9 months</td>
<td>41%</td>
</tr>
<tr>
<td></td>
<td>500 mg cisplatin</td>
<td>365</td>
<td>49.7%</td>
<td>9.9 months</td>
<td>43%</td>
</tr>
<tr>
<td>INT ACT 2</td>
<td>250 mg 1st line with paclitaxel</td>
<td>347</td>
<td>30.0%</td>
<td>8.7 months</td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td>500 mg paclitaxel and carboplatin</td>
<td>345</td>
<td>30.4%</td>
<td>9.8 months</td>
<td>41%</td>
</tr>
</tbody>
</table>

The current indication of Iressa is treatment of patients with locally advanced or metastatic NSCLC who have failed prior therapy. The data is relatively mature. The IDEAL 1 and 2 studies were the pivotal studies that led to FDA approval in May 2003. Both studies enrolled only patients with recurrent or refractory disease after one or two lines of chemotherapy. The role of Iressa as first line therapy remains unclear. To date there are over 100 000 patients treated with Iressa in the world. Over 1 000 patients received the drug within clinical trial setting with detail documentation on all drug-related adverse events and the others in the Expanded Compassionate Program or as a marketed drug. Extensive toxicity data is available. The most frequently reported adverse events at dose level of 250 mg daily were diarrhea, skin rash, acne and asthenia. Most were mild and reversible upon cessation. NCI-CTC grade III and IV diarrhea and acne occurred in about 3% of patients. Other serious but uncommon toxicities included conjunctivitis, cardiovascular event, prolongation of QT interval and interstitial lung disease (ILD). Up to December 2002 there were 358 cases of ILD reported in Japan (estimated incidence 1.9%) and 84 cases in other countries (estimated incidence 0.32%). Mortality rate was 0.6% and 0.1% respectively. The median time of onset was 24 days in Japan and 42 days in other countries. There is no specific pre-disposing factor except for the higher incidence in Japan. However, patients with prior idiopathic pulmonary fibrosis are at higher risk of death related to ILD. Over 90% of patients with ILD presented with symptoms including fever, dry cough, dyspnea or melaena. Early diagnosis can be captured by plain chest X-ray and arterial blood gas. The most common CT scan finding is patchy diffuse ground glass shadow but this non-specific image cannot exclude infection. Treatment for Iressa related ILD includes immediate discontinuation and/or steroid pulse therapy. The pathology of autopsied patients showed diffuse alveolar damage, however, the mechanism of injury remains unclear. The element of ethnic difference also remains unclear.

In summary, Iressa is the first EGFR inhibitor with established efficacy as second or third line therapy for advanced NSCLC. Toxicity profile is mild with the only exception of ILD which is uncommon and reversible if detected early.

### 3 Antiangiogenesis

Angiogenesis is an essential physiological process for tumor growth. It is a complex multistep process that involves degradation of basement membrane matrix...
ngation of endothelial cell and vessel proliferation\(^{[17]}\). A cascade of endogenous inhibitors and promoters inter-
plays to assure appropriate and controlled growth of the vessel. Examples of the endogenous inhibitors include
angiostatin, endostatin, interleukin (1, 6 and 12), platelet factor 4 and thrombospondin. Examples of the
promoters include angiotropin, fibroblast growth factor, interleukin 8 and matrix metalloproteinases (MMPs). In principle,
manipulation of these endogenous substances may alter the pattern of vessel growth. Recent investigation has
focused on inhibition of the endogenous promoters such as MMPs and vascular endothelial growth factors
(VEGF) as the prime target of antiangiogenesis therapy for lung cancer.

The first step in angiogenesis requires degradation of
the extracellular matrix and basement membrane\(^{[18]}\). The MMPs are the essential endopeptidases for degrada-
tion of basement membranes. They also play the crucial role of interacting with VEGF. There are more than 30
MMPs and each substrate has its own function and pattern of expression. For NSCLC MMP-2 and MMP-9
are frequently overexpressed and their over-expression are considered to be a poor prognostic indicator\(^{[19]}\).

AG3340 (Prinomastat) is an inhibitor of MMP-2 and MMP-9 with specific antiangiogenesis effect in NSCLC. However, two multicenter comparative studies, where it was added to either paclitaxel and carboplatin, or gemcitabine and cisplatin have reported no survival benefit\(^{[20, 21]}\). Marimastat is an oral board spectrum MMP inhibitor (against MMPs 1, 2, 3, 7, and 9) that was extensively studied\(^{[22]}\). A study of the drug on small cell lung cancer patients who had responded to chemotherapy reported no survival benefit. About 20% of patients had significant musculoskeletal toxicity that required early discontinuation\(^{[23]}\). New MMP inhibitors with a more specific target are being developed.

VEGF also plays key role in vascular permeability, apoptosis and metastatic potential\(^{[25]}\). Inhibition of
VEGF leads to cessation of tumor growth in a variety of cancer cell line. RhuMAb VEGF (Bevacizumab,
Avastin) is a recombinant monoclonal antibody against the VEGF receptor. Preclinical studies of these drugs have
demonstrated tumor inhibition and potential synergistic effects with cytotoxic therapy\(^{[26]}\). Monotherapy of
Avastin has been shown to prolong time to disease progression in patients with metastatic renal cell carci-
 noma\(^{[27]}\). Its role in NSCLC remains to be explored. A phase II trial randomized patients with advanced
NSCLC to chemotherapy (paclitaxel and carboplatin) alone or same chemotherapy with either low or high
dose of Avastin\(^{[28]}\). The response rate was 31.3%, 21.9% and 40%, respectively. There was a small survival
benefit associated with the high dose arm of 17.7 months versus 14.9 months in the control arm. Note-
worthy is the unexpected life threatening hemoptysis is associated with centrally located and squamous cell tumor.

A large phase III study is now ongoing through the Eastern Cooperative Oncology Group, which random-
ized patients to receive chemotherapy with or without Avastin at 15 mg/kg. Patients with history of hemopty-
sis or squamous cell histology are excluded. Primary endpoint is survival and crossover of patient is not al-
lowed.

SU5416 (Sugen) is a quinolone derivative that can inhibit the VEGFR-2. The drug is associated with sig-
nificant risk of vascular events such as pulmonary emboli and myocardial infarct when given with gemcitabine and
cisplatin\(^{[29]}\). These toxicities have prevented further investigation in combination therapy for lung cancer. There are a number of other new agents with antiangiogenic activity including ZD6474, CP547632, SU6668, AD941, TNP470 and squalamine but none has attained a significant role in the management of lung cancer. In
summary, combinations of MMP inhibitor with chemotherapy have failed to show a benefit while the
combination of Avastin and chemotherapy may hold the promise to improve the outcome of lung cancer patients.
4 Antisense oligonucleotides

Antisense is a novel technology that enables the silencing of a cancer-specific gene at the functioning level\(^{30}\). Recent advances in automated DNA synthesis have led to rapid progression of the antisense technology. Antisense oligonucleotides are strands of modified DNA with 18 to 20 nucleotides that can bind to mRNA and form a hybrid area that is subjected to degradation by RNase H. As results of inhibition of RNA transport and translation, the antisense oligonucleotides may stop protein synthesis. A number of genes are potential targets for antisense oligonucleotides, which include the PKC-α, Bcl-2, c-Raf and c-Myb. One of the best developed agents is Affinitak (LY900003), an antisense inhibitor of protein kinase C-alpha (PKC) by ISIS and Eli Lilly. PKC are a group of phospholipids dependent isoenzymes responsible for signal transduction. PKC-α is commonly over-expressed in human tumors and plays the crucial role of signal transduction\(^{31}\). This protein is essential in tumor apoptotic pathway and gene synthesis. Inhibition of PKC may promote tumor cell death and sensitize the chemotherapeutic effects. In a phase I study of 21 patients with advanced cancer Yuen et al\(^{32}\) documented the dose limiting toxicity of thrombocytopenia and fatigue. The maximum tolerated dose was 2 mg/kg per day. Combination of taxol/carboplatin with Affinitak has showed promising response rate in an extended phase I-II study\(^{33}\). Fifty-three patients were recruited with tumor response rate at 46% and median survival of 15.9 months. Based on these encouraging results two phase III randomized studies comparing combination of chemotherapy and Affinitak to chemotherapy alone were performed. However, preliminary data of both studies have failed to show a survival benefit. The final reports are still pending.

Another antisense oligonucleotide targets the Bcl-2, a key apoptotic gene. It is a proto-oncogene located at the breakpoints of t(14; 18) chromosomal translocations in lymphoma\(^{34}\). The Bcl-2 and Bcl-xl interact in the carcinogenesis of solid tumors including NSCLC and many tumor cells have co-expression of both. A phase I study of an antisense oligonucleotide of the first 6 codons of Bcl-2 on 21 patients with lymphoma reported the dose limiting toxicity of thrombocytopenia and hypertension. No clinical study on lung cancer has been reported yet. The Raf is another important proto-oncogene encoding a kinase for the downstream pathway of MAPK\(^{35}\). ISIS5132 is the antisense oligonucleotide targeting this site. A phase I study on patients with refractory solid tumor showed the drug to be well tolerated and early tumor responses were observed\(^{36}\).

5 Proteasome inhibitor

A number of cellular processes, including cell cycle regulation, signal transduction, gene transcription and apoptosis depend on the ubiquitin-mediated protein degradation. The activation and deactivation of these processes are regulated by degradation of the associated protein\(^{37}\). The 26S proteasome is the key ATP-dependent protease that is responsible for degradation of proteins conjugated to the polypeptide ubiquitin.

PS-341 (Velcade) is a potent inhibitor of the 26S proteasome. Its tumor suppressing effect is mediated via a number of molecular targets including p27, p53, Bcl-2, Bax and cyclin D. Pre-clinical study on NSCLC reported IC50 of 7 nmol/L. A phase I-II study on 53 patients with advanced solid tumors has identified the MTD at 1.86 mg/m\(^2\)\(^{38}\). The dose limiting toxicities were diarrhea, fatigue and hypotension. Other side effects including peripheral neuropathy, headache, edema and ileus were less severe and more uncommon. One partial response and two stable diseases were reported in this MD Anderson study. Another phase II study used the twice weekly regimen on 43 patients with advanced solid tumor\(^{39}\). Dose limiting toxicities were diarrhea and neurosensory toxicity. One patient with bronchioalveolar carcinoma had a partial response. Phase II studies on combination of PS-341 with gemcitabine or docetaxel are ongoing.
6 COX-2 inhibitor

COX-2 inhibitor is a potential anti-neoplastic agent[40]. Early data on the role of COX-2 enzyme in carcinogenesis of colorectal cancer yield important information on the eicosanoid pathway[41]. Eicosanoids are the oxidated products of arachidonic acid. The COX enzymes are responsible for conversion of arachidonic acid to prostaglandins and thromboxane, which hold an extensive functional profiles that include regulation of renal blood flow, control of inflammatory process and stimulation of pain fibers. More specific to lung cancer, the COX-2 inhibition rate was 24%. Toxicities were not dissimilar to nation of docetaxel and celecoxib in surgery if feasible. Tumor response rate was 75% and after two cycles of therapy, patients were subjected to coxib with taxol/carboplatin as neo adjuvant therapy. Many studies on novel molecular targeted therapies for NSCLC have shown encouraging results. Iressa, the first EGFR inhibitor, is now the standard third line treatment for advanced NSCLC. Its roles as first line therapy and adjuvant therapy are being investigated. Antiangiogenesis using MMP inhibitor has been a disappointing exercise. However, Avastin holds the future promise to effective antiangiogenesis. Other specific pathways are potential targets on which extensive investigations are ongoing.

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