Targeted lung cancer therapy: what have we learned from gefitinib?

Peilin Zhang [†] ***& John Rogers***

[†]Author for correspondence
Putnam General Hospital Laboratory, 1400 Hospital Drive, Hurricane, WV 25526, USA
Tel: +1 304 757 1768
Fax: +1 304 757 1736
Peilin.Zhang@hcahealthcare.com

'Gefitinib in lung cancer and imatinib in CML mark the beginning of a new era for cancer treatment – targeted cancer therapy.'

Lung cancer is the leading killer of all cancer patients, accounting for 28% of all cancer deaths. Lung cancer is classified histologically as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) including adenocarcinoma, squamous carcinoma and other subtypes. SCLC represents approximately 20% of lung cancers, and NSCLC represents the remaining 80%. Based on cancer statistics from the American Cancer Society, there were 175,000 new cases of lung cancer in the USA and approximately 165,000 lung cancer deaths in 2004. Unlike other common cancer types, there appears to be a tight correlation between lung cancer incidence and death, indicating the poor outcome regardless of treatment modalities.

Traditionally, early stage NSCLC (Stage I, II and IIIA) has been treated with surgical resection when possible. Adjuvant chemotherapy is recommended after surgery. Locally advanced NSCLC (some stage IIIA and stage IIIB) is generally treated with radiation combined with chemotherapy. Patients with distant spread (stage IV) receive palliative chemotherapy, usually consisting of one cytotoxic drug such as paclitaxel, doceptaxel or gemcitabine combined with a platinum derivative. There have been a number of regimens evaluated in clinical trials without demonstration of one clearly superior treatment regimen in regard to patient survival [1]. Clearly, new treatment approaches are needed to improve patient survival in lung cancer.

There are emerging products based upon the recent advances of molecular biology of human cancers. Unlike cytotoxic chemotherapy drugs, these new agents target molecular signaling pathways within the cancer cells and show promise in a variety of cancers. Imatinib (STI-571, Gleevec®, Glivec®, Novartis Pharma), the first of the targeted agents, is an inhibitor of cytoplasmic c-Abl kinase approved by the US Food and Drug Administration (FDA) in 2001. Imatinib has showed significant clinical benefit in patients with chronic myelogenous leukemia (CML) with positive Philadelphia chromosome and the BCR-ABL fusion gene [2,3]. Imatinib induces both hematological and molecular remission in CML patients [3]. This is the first drug that specifically targets a regulatory molecule within the cancer cells leading to clinical remission of cancer patients. Subsequently, gefitinib (Iressa®, ZD1839) from AstraZeneca, was developed for NSCLC [4–6] using a very similar principle and technology to imatinib. Gefitinib is a synthetic small organic molecule targeting the intracytoplasmic domain of the epidermal growth factor receptor (EGFR) which is expressed in a variety of normal human tissues and cancers [7]. The binding of gefitinib to EGFR prevents intracytoplasmic signaling by inhibiting intrinsic tyrosine kinase activity, thus blocking the growth-promoting effect of the EGFR (tumor cell proliferation). Based on cell culture studies, gefitinib would be potentially useful for cancers with high expression of EGFR, such as squamous cell carcinoma of the lung, squamous cell carcinoma of the head and neck, glioblastoma multiforme and others [4,7]. Initial clinical data suggests otherwise. Multicenter clinical trials on NSCLC, including squamous cell carcinoma and adenocarcinoma ,showed that only a small fraction of NSCLC patients responded to gefitinib with tumor shrinkage [4]. Many of those responding to the drug were non-smoking women with adenocarcinoma, especially with bronchioalveolar features. Responding patients represent approximately 10% of the total of NSCLC population. Following this clinical observation, two independent groups simultaneously discovered the underlying molecular mechanism by which gefitinib exerts its function. They selected the gefitinib-responsive patients, extracted the genomic DNA from patient tumor samples and sequenced the entire EGFR gene. Remarkably, clusters of EGFR mutations were uncovered within exons 19 to 21 of the EGFR gene from the majority of gefitinib-responsive tumors, but not from gefitinib-resistant tumors. Gene mutations were found within the activation loop of the tyrosine kinase domain of EGFR. The most common mutations were small in-frame deletions or amino acid substitutions within this region [8,9]. Furthermore, the mutations

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from the gefitinib-responsive tumors were heterozygous, suggesting a gain-of-function mutation. Mutations of this activation loop of the EGFR sequence rendered the receptor significantly more sensitive to ligand binding and cellular signaling function [8–10].

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Interestingly, further work demonstrated that these mutations activated downstream targets such as AKT and signal transducers and activators of transcription (STAT) signaling pathways, promoting cell survival instead of cell proliferation, a conventional function of EGFR [11]. The mutated EGFR is significantly more susceptible to gefitinib inhibition than the wild-type counterpart [8,9,11]. These discoveries not only revealed the mystery of gefitinib response, but also changed the fundamental view of lung cancer biology and carcinogenesis. This finding indicates that first, a small percentage of NSCLC is caused by and dependent upon a single somatic gain-of-function mutation of a single gene, EGFR; and second, targeting the mutant gene by inhibition through small organic molecules can lead to control of the tumor and clinical remission. This is the first solid tumor to demonstrate a response to targeted therapy for a membrane receptor-based cellular signaling pathway. A similar therapeutic mechanism was discovered for gastrointestinal stromal tumor (GIST) and imatinib approximately a year ago [12,13].

From a histopathology point of view, human solid tumors are heterogeneous in nature with significant variations in morphology, growth and differentiation among the same histologic types of tumor. At the molecular levels, although many genes were discovered to be mutated in the tumors, the key regulatory gene(s) which serve as a driving force for tumor growth/antiapoptosis in about 90% lung cancers remain to be discovered. Gefitinib in lung cancer and imatinib in CML mark the beginning of a new era for cancer treatment – targeted cancer therapy. This is an exciting time for close collaboration between basic scientists and clinical oncologists. An optimal interdisciplinary approach including medical oncologists, surgical oncologists, radiation oncologists, histopathologists and basic molecular oncologists will be needed to explore the growing field of molecular biology and targeted therapy.

Discovery of the EGFR mutation within NSCLC is certainly exciting in regard to understanding lung cancer carcinogenesis and molecular response to gefitinib. It also raises the question of the importance of determining EGFR mutation status before gefitinib is administered for the treatment of NSCLC patients. Indeed, patients may request to know their EGFR mutation status before taking gefitinib. Determination of EGFR mutation status will involve technical and quality assurance issues. It should be noted that erlotinib (Tarceva®, OSI 774, OSI Pharmaceuticals), a similar drug to gefitinib, has recently been approved by the FDA for the treatment of NSCLC patients.

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