Personalised Therapy with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Non–small-cell Lung Cancer: Consensus and Controversy

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ABSTRACT
The epidermal growth factor receptor tyrosine kinase inhibitors, including gefitinib and erlotinib, have been proven to provide significant benefit in progression-free survival and overall survival in patients who have received at least one line of prior chemotherapy. Subgroup analyses of previous placebo-controlled clinical trials demonstrated that epidermal growth factor receptor mutation–positive status was associated with improved outcomes with epidermal growth factor receptor tyrosine kinase inhibitor therapy, leading to further investigation of these agents in the first-line setting. However, selection by clinical characteristics has proved inadequate for identifying all patients with epidermal growth factor receptor mutation–positive disease. Recently, several randomised and multicentre phase III clinical trials investigated the efficacy and tolerability of first-line gefitinib or erlotinib versus standard chemotherapy regimens in patients with confirmed epidermal growth factor receptor–activating mutation non–small-cell lung cancer. The results demonstrated that epidermal growth factor receptor mutation is a key to achieving exceptional outcomes with tyrosine kinase inhibitor therapy, regardless of patient clinical characteristics. However, there are also some dilemmas in genotype-based personalised tyrosine kinase inhibitor treatment. It is not yet clear whether this approach should only be applied after standard first-line chemotherapy or be used as first-line therapy to start with. In addition, as a non-invasive and repeatable source of genotypic information, it is uncertain whether repeated determination of epidermal growth factor receptor mutation status in peripheral blood could be helpful. In future, more clinical studies combined with prospective molecular analysis are warranted to verify the best strategy for individualised target therapy in selected patients with non–small-cell lung cancer.

Key Words: Carcinoma, non-small-cell lung; Lung neoplasms; Protein-tyrosine kinases; Receptor, epidermal growth factor; Survival rate

中文摘要
表皮生長因子受體酪胺酸激酶抑制劑對非小細胞肺癌患者的個體化治療：共識與爭議
卓明磊、王潔

表皮生長因子受體（EGFR）酪胺酸激酶抑制劑（TKI）類藥物，包括gefitinib及erlotinib，已被證實為至少已經接受一線化療的病人提高無惡化生存期及總生存時間。採用安慰劑對照的臨床研究的亞組分析顯示，EGFR突變狀況與EGFR-TKI治療帶來的改善有關，令至有更多關於使用EGFR-TKI作一線治療的研究。儘管如此，純粹用臨床特徵辨別所有具EGFR突變的病人並不足夠，最近有幾個隨機及多中心III期臨床研究探討在確認有EGFR突變的非小細胞肺癌患者中，比較標準化療及使用

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INTRODUCTION
Lung cancer is still the leading cause of cancer death worldwide; non–small-cell lung cancer (NSCLC) is the most common form and accounts for approximately 85% of cases.2,3 Traditional chemotherapies have reached a plateau in terms of efficacy.4-6 Developments in molecular research show that we can no longer assume one therapeutic regimen is fit for all such patients. Survival rates not only depend on the efficacy of treatments but also on the genetic makeup of each individual and the type of tumour that one has. With the study and discovery of biomarkers and epidermal growth factor receptor (EGFR) therapy, survival rates for patients with NSCLC have been increasing.

In some tumours including NSCLC, it is evident that EGFR is over-expressed. Activation of EGFR tyrosine kinase leads to activation of several signal pathways including the Ras/MAPK pathway and the PI3K/Akt pathway, which drive malignant transformation. In a subset of patients with NSCLC, treatment with reversible EGFR tyrosine kinase inhibitors (TKIs) results in dramatic antitumour activity. Sequencing of the EGFR gene revealed that the majority of tumours responding to EGFR TKIs harboured mutations in the TK domain of EGFR.7-9

EGFR-activating mutation–based EGFR-TKI first-line therapy has become the model of personalised treatment, which indicates that we are entering an era of individualised therapy for NSCLC. In this article, the latest data on EGFR-TKI studies are reviewed, and consensus and controversies about personalised EGFR-TKI therapy are discussed.

EGFR MUTATIONS IN CHEMOTHERAPY-NAÏVE NSCLC: TARGETING NEW DISEASE
Selection of therapy for patients with advanced-stage NSCLC remains largely empiric. Although a number of potential predictive biomarkers for both chemotherapy and targeted therapies have been reported within the last several years, till now very few have proven to be ‘practice-changing’. However, with the advent of first-line EGFR-TKI therapy for the patients with known activating mutations in EGFR, this situation has now changed.

The large phase III trial of gefitinib versus paclitaxel/carboplatin in Asia (IPASS) recruited 1217 patients in East Asian countries, who were selected on the basis of clinical (including adenocarcinoma) characteristics, non-smoker or light-smoker status.10 This study achieved its primary endpoint by demonstrating gefitinib’s noninferiority, and with respect to its impact on progression-free survival (PFS), it was also superior (hazard ratio [HR] for gefitinib vs paclitaxel/carboplatin = 0.74; 95% confidence interval [CI], 0.65-0.85; p < 0.001). HR in this paper refers to the risk of adversity relative to the comparator. The 12-month rates for PFS were 24.9% with gefitinib and 6.7% with standard chemotherapy. In the subgroup of patients harbouring the EGFR mutation, gefitinib achieved a significantly longer PFS than chemotherapy (HR = 0.48; p = 0.0001). By contrast, in patients who were negative for the mutation, PFS was significantly longer in chemotherapy group (HR = 2.85; p < 0.001). The objective response rates were 71.2% and 1.1% for first-line gefitinib in patients with and without EGFR mutation, respectively. Such results indicated that gefitinib could be used as first-line therapy for patients carrying EGFR-activating mutation, while those without the mutation should receive standard chemotherapy.

A Korean study (First-SIGNAL) with a similar design to IPASS randomised 313 patients with adenocarcinoma who were non- or light-smokers into gefitinib or a gemcitabine-plus-cisplatin regimen.11 The primary endpoint was overall survival (OS). Despite there being no significant difference in OS in the 2 treatment arms, the study provided supportive evidence about the importance of EGFR mutation–positive status, as such patients enjoyed a higher tumour response rate and prolonged PFS with gefitinib therapy.