



Oral Treatment for Advanced Lung Cancer - The Story of Iressa

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1. Introduction

Lung cancer is the leading cause of cancer death in approximately 1.1 million of people worldwide. In Hong Kong, the death toll from lung cancer in 2001 was 3269. More than 80% of lung cancers are thought to be related to smoking. There are 2 major histopathological types: small cell lung cancer (20%) and non small cell lung cancer (NSCLC) (80%). For the early stages of disease (TNM Stage I, II and IIIA), surgery, radiotherapy and chemotherapy can be offered alone or in combination. For the advanced Stages (TNM Stage IIIB or IV), chemotherapy is the cornerstone of therapy.

2. Chemotherapy for Advanced NSCLC

In the last decade, we see the introduction of newer anticancer agents, such as gemcitabine, taxanes, vinorelbine and irinotecan, with promising activity when given with cisplatin or carboplatin. These doublets achieve a median survival of approximately 8 months and a 1 year survival rate of 35%.

As more patients receive first-line chemotherapy, the demand for effective second line and third line treatment has emerged.

3. Rationale for targeting the epidermal growth factor receptor (EGFR)

EGFR belongs to a family of 4 closely related cell surface receptors:

EGFR (HER₁ or erbB₁)

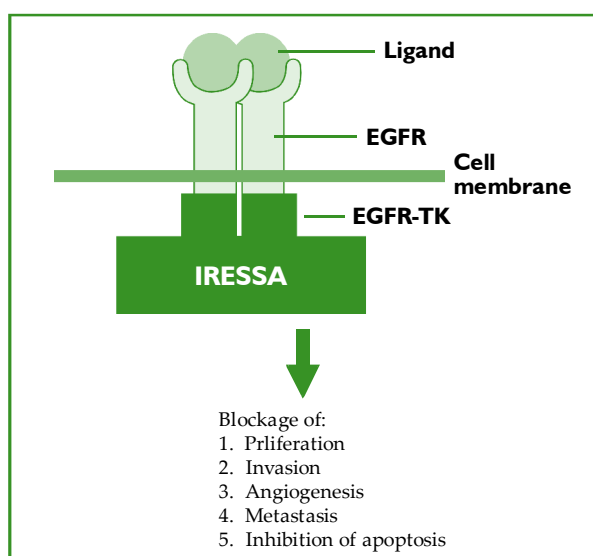
erbB₂ (HER₂-neu)

erbB₃ (HER₃)

erbB₄ (HER₄)

These receptors are transmembrane glycoproteins sharing a common structure consisting of an extracellular ligand-binding domain, an intramembranous domain and an intracellular tyrosine kinase domain. The EGFR pathway is implicated in several aspects of tumour survival and growth.

Iressa (gefitinib) is an orally active EGFR tyrosine kinase inhibitor (EGFR-TKI) that blocks signal transduction pathways responsible for cellular proliferation.

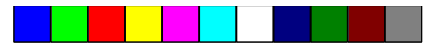


Iressa, the only biological agent currently licensed for use in NSCLC as a third line therapy, has encouraged active treatment rather than just offering best supportive care to these patients.

4. Clinical experience

Iressa data are available from two large, randomised, double-blind Phase II trials in patients suffering from locally advanced or metastatic NSCLC (IDEAL 1 and IDEAL 2). Patients in IDEAL 1 had 1 or 2 previous chemotherapy regimens of which a platinum is included. Patients in IDEAL 2 had 2 or more regimens using platinum and docetaxol separately or concurrently. The objective response rates of 18.4% and 12% with an overall disease control rate (response + stable disease) of 54.4% and 42.2% were quoted for IDEAL 1 and IDEAL 2 respectively.

However, data available in Dec 2004 from ISEL Trial (1692 patients from 28 countries) failed to show improvement in overall survival for Iressa in comparison to best supportive care. (Median survival 5.6 vs 5.1 months). Of interest is the finding that oriental patients had an improvement in survival (Median survival 9.5 vs 5.5 months p=0.01) and non smokers had an improvement in survival (Median survival 8.9 vs 6.1 month p=0.01).



Most of the patients who respond did so rapidly. The median duration of response for IDEAL 1 was 13 months and for IDEAL 2 was 7 months. The 1 year survival rates were 35% and 27% for IDEAL 1 and IDEAL 2 respectively. These data compare favourably with that of docetaxel (37%) used as second line therapy. Furthermore, an improvement in disease-related symptoms was associated with an increase in overall survival.

5. Side effects

Iressa 250mg daily orally has a mild side effect profile. The most commonly reported adverse drug reactions include skin rash, diarrhoea, dry skin, acne, nausea and liver function test abnormalities. Interstitial lung disease has been observed uncommonly in some cases, especially in Japan.

6. Predicting Response

Lynch et al reported in 2004 specific somatic EGFR mutations in the tyrosine kinase domain in a subset of patients who dramatically benefit from Iressa. As symptom improvement occurs with a median time to onset of 8-10 days, this is perhaps the most reliable predictor of clinical benefit with Iressa.

7. Economic Implications

Hospitalisation for administration of chemotherapy and toxicity management is costly in lung cancer treatment. Best supportive care is not inexpensive too. Hence the efficacy, tolerability and oral administrations of Iressa is economically sound. The improvement of quality of life for the terminally ill lung cancer patients should not be underestimated.

Suggested readings

1. Fukuoka M, Yano S, Giaccone G et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2003; **21**:2237-2246
2. Herbst RS. ZD1839: targeting the epidermal growth factor receptor in cancer therapy. *Expert Opin Investig Drugs* 2002; **11**:837-849
3. Kris MG, Natale RB, Herbst RS et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer. A randomized trial. *JAMA* 2003; **290**:2149-2158.
4. Lynch TJ, Bell DW, Sordella R et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004; **350**:2129-2139.
5. Schiller JH, Harrington D, Belani CP et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002; **346**:92-98.



Clinical Quiz

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Clinical Information:

- 4 years old girl
- Incidental finding of opacity at right mediastinum in routine chest X-ray.
- This is her post-contrast CT thorax.

Question:

- What are the radiological findings ?
- What is your diagnosis ?
- Any further investigation.

(See P22 for answers)

