

The gefitinib story

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Gefitinib (Iressa, ZD1839, AstraZeneca Japan) was approved by the Japanese Ministry of Health, Labor and Welfare (MHLW) in July 2002 for the treatment of inoperable or recurrent non-small cell lung cancer (NSCLC). In Japan, up until the end of January 2003, approximately 23 500 people had received gefitinib and 183 deaths had been attributed to the drug. Acute lung disease and/or interstitial pneumonitis were implicated in 173 deaths. In this article we shall give a brief description of gefitinib, an outline of the experience with this drug in Japan and in Western countries, and also our opinion on what should be learnt from this story.

Mechanism of action

Epidermal growth factor receptor (EGFR) is a cell surface receptor. Tyrosine kinase acts on this receptor within the cell to regulate cell proliferation and survival. Inactivation of EGFR by tyrosine kinase inhibition induces apoptosis (cell death), and reduces angiogenesis and metastasis of cancer cells.^{1,2}

During anticancer therapy research, AstraZeneca researchers noted that:

1. there was an increased EGFR-mediated drive in a variety of solid tumours (eg NSCLC, breast cancer)
2. excessive activation of EGFR on the cancer cell surface was associated with advanced disease and a poor prognosis in cancer patients.

Inactivation of EGFR therefore became a target for anticancer therapy. AstraZeneca screened 1500 EGFR-tyrosine kinase inhibitor (TKI) derivatives and developed the orally active gefitinib as the most selective inhibitor.³

Effect on normal cells

AstraZeneca has stressed gefitinib's EGFR-TKI selectivity and its efficacy on experimental tumour models.¹⁻³ However, they have not adequately addressed the potentially harmful effects on normal tissue and injured noncancer cells.

Almost all cells have EGFRs.⁴ So gefitinib not only inhibits the growth of cancer cells but also inhibits physiological replacement of normal cells, particularly after injury when recovering tissues require more epidermal growth factor.

This effect has been demonstrated in animal models. Studies in mice and rats with

deficient levels of EGFR have shown impaired epithelial development in several organs, including skin, lung and gastrointestinal tract⁴, severe bleeding and weight loss in newborn rats with laboratory-induced necrotising enterocolitis⁵, and delayed corneal wound healing.⁶

Animal toxicity studies

Six-month toxicity studies in dogs revealed an increase in hepatic necrosis after gefitinib was given at doses of 5 mg/kg/day, which approximates the clinical dose in humans. When doses of 15 mg/kg/day were given after 10 days at 25 mg/kg/day, relative lung weight and white blood cell counts in dogs increased dose-dependently³, indicating lung inflammation that was possibly induced by gefitinib.

In 6-month rat studies, 4 of 60 rats died after being given gefitinib at a dose of 25 mg/kg/day for 8 weeks followed by 15 mg/kg/day for 4 months.³ The rats were shown to have renal papillary necrosis, liver necrosis and other lesions. These findings were considered to be consistent with the mechanism of action of gefitinib.³

It was reported recently in the Japanese press that AstraZeneca did not submit the

results of a series of animal experiments that showed gefitinib increased bleomycin-induced lung toxicity (alveolar damage and fibrosis).⁷ This is currently being investigated by the MHLW.⁸

Clinical Trials

IDEAL 1 and IDEAL 2

Results of two randomised double-blind phase II trials (IDEAL 1⁹ and IDEAL 2¹⁰) were presented at the American Society of Clinical Oncology (ASCO) meeting in May 2002.

IDEAL 1 (AstraZeneca Study 16) enrolled 210 patients with locally advanced or metastatic NSCLC who had previously received at least one chemotherapy regimen containing platinum.

IDEAL 2 (AstraZeneca Study 39) enrolled 216 patients (mostly Caucasians) with locally advanced or metastatic NSCLC who had previously failed at least two prior chemotherapy regimens containing platinum and docetaxel therapy. In both trials, patients received gefitinib orally at a dose of either 250 mg daily or 500 mg daily. Response and survival rates are shown in Table 1 below.

Table 1. Tumour response rate and median survival in patients treated with gefitinib after previous treatment with platinum-based chemotherapy

	IDEAL 1 (Study 16)		IDEAL 2 (Study 39)	
	250 mg/day	500 mg/day	250 mg/day	500 mg/day
Objective tumour response rate	18.4%	19.0%	11.8%	8.8%
Median survival (months)	7.6	8.1	6.1	6.0

A subsequent evaluation of Study 16 by the Japanese Pharmaceutical and Medical Devices Evaluation Centre showed that the response rate in Japanese patients (23.5% in both 250 mg and 500 mg arms) was higher than in non-Japanese patients (5.8% in 250 mg arm, 9.3% in 500 mg arm). Although the reason for this difference is not entirely clear, the less intensive and shorter duration of chemotherapy regimens often used in Japanese patients may influence the response to subsequent therapy.

Adverse reactions

In Study 39 the most frequent adverse events in patients receiving 250 mg gefitinib daily were diarrhoea (57%), rash (48%), asthenia (28%), dyspnoea (28%), nausea (27%) and acne (26%).¹¹

The mortality rate in this study due to adverse events was reported as 5.1% (11/216).^{3,11} However, another 4 deaths due to adverse events—pneumonia (1), acute respiratory distress syndrome (ARDS) (1), dyspnoea (2)—were described in a note outside the relevant table. The true mortality rate due to adverse events was therefore almost 7% (15/216).

Serious adverse events such as ARDS and/or pneumonia or pneumonitis (or acute lung injuries) were seen in 55 of the 216 patients (25%) in Study 39 and in 39 of the 107 Caucasian patients (36%) in Study 16. Of these, 15 patients (6.9%) in Study 39 and 4 Caucasian patients (3.7%) in Study 16 died due to adverse events.

In one of the phase I/II trials (AstraZeneca Study 11), 9 of 69 patients (13%) died due to an adverse event. Of these, 7 had respiratory tract complications: pulmonary insufficiency (2), pneumonia (2), bleeding from respiratory tract (2), and ARDS (1). Of the 9 deaths due to adverse events, gefitinib had been withdrawn in 5 of the patients, but none of these events were classified as drug-related.

INTACT 1 and INTACT 2

Results of two large randomised, double-blind, placebo-controlled, phase III trials in chemotherapy-naïve patients with advanced

NSCLC were presented at the European Society for Medical Oncology Congress in October 2002.^{12,13}

Gefitinib (250 mg/day or 500 mg/day) or placebo was combined with gemcitabine and cisplatin in INTACT 1 (1093 patients)¹² and with paclitaxel and carboplatin in INTACT 2 (1037 patients).¹³

Neither study showed an improvement in response rate or survival benefit when gefitinib was added to standard treatment.

Pharmacokinetics

Gefitinib is mainly metabolised by liver CYP3A4. CYP3A4 activity varies more than 40-fold between individuals.^{14,15}

Subsequently, there is wide (30- to 100-fold) interindividual variation in maximum concentration and area under the curve values after repeated gefitinib dosing.³ Time to maximum concentration (T_{max}) in cancer patients varied from 1 to 24 hours and elimination half-life varied from 10 to 90 hours in healthy volunteers and patients.³

Japanese experience

Gefitinib was approved on 5 July 2002 in Japan, five months after the application was submitted by AstraZeneca.

On 15 October 2002, the Japanese MHLW issued a 'yellow letter' alerting prescribers that the use of gefitinib had been linked to 13 deaths. More detailed adverse effect warnings were also imposed at this time.

However, the mortality rate continued to rise, with 124 deaths due to adverse reactions to gefitinib notified by 13 December 2002. Stricter safety measures were announced by the MHLW on 26 December 2002. These measures were recommended by a panel, comprising experts in medicine and pharmacy, which had been convened to examine the safety of gefitinib.

The new measures require that:

- informed patient consent must be obtained before gefitinib is administered
- gefitinib must only be prescribed by doctors experienced in treating patients with lung cancer

- patients must remain in hospital for four weeks after the commencement of therapy
- doctors must exercise caution in using gefitinib in patients who have a history of interstitial pneumonitis or other lung diseases.

In February 2003, AstraZeneca Japan announced that the number of deaths as a result of adverse reactions to gefitinib in Japan had reached 183 by 31 January 2003.¹⁶ Approximately 23 500 patients had received gefitinib in Japan by this date, and there had been 644 adverse reaction reports. Of these, acute lung disease and/or interstitial pneumonitis were implicated in 473 cases and, of these, 173 patients had died.

AstraZeneca Japan claims that the safety measures introduced by the MHLW on 26 December 2002 have effectively decreased the case mortality rate but the cumulative mortality rate continues to rise.

Case reports

The following cases were presented to the Japanese panel considering the safety problem of gefitinib in late 2002.⁸

Case 1. A woman in her sixties was admitted with progression of lung cancer. Three weeks after admission, treatment with gefitinib was commenced. Her lung cancer responded well and her tumour decreased in size within one week, but the next day she had diarrhoea and dyspnoea. Typical diffuse opaque appearance on the chest X-ray was found and gefitinib was withdrawn. She failed to improve with oxygen and corticosteroid pulse therapy. She died 8 days after the withdrawal of gefitinib from multiorgan failure involving lung, gastrointestinal tract, liver, kidneys and heart.

Case 2. An ambulant woman in her seventies with NSCLC was admitted to hospital and gefitinib therapy was initiated the next day. Seven days later, the woman complained of dyspnoea and a chest X-ray indicated interstitial pneumonitis. Gefitinib was withdrawn and she was treated with corticosteroids, but she died later that day.

Case 3. A man in his seventies with severe congestive heart failure experienced abdominal discomfort the evening after commencing gefitinib. On day 3, he developed an ileus and gefitinib was withdrawn. However, severe hypoxaemia and pulmonary symptoms progressed. He died one week after the withdrawal of gefitinib with multiorgan failure involving the lungs, gastrointestinal tract, and kidneys. The elimination of gefitinib by CYP3A4 liver and intestinal enzymes may have been compromised in this patient as a result of his severe congestive heart failure.

The panel noted that of the 17 patients who experienced adverse symptoms within one week of commencing gefitinib, 13 (76%) died.

Published case reports

An article published in *The Lancet* in January 2003 described four Japanese patients with advanced NSCLC who developed severe acute interstitial pneumonia in association with gefitinib.¹⁷ Two patients recovered but the other two died from progressive respiratory dysfunction. The authors concluded that gefitinib induces pulmonary toxic effects, especially in patients with pulmonary comorbidities.

AstraZeneca response

AstraZeneca has queried the association between gefitinib and the deaths in Japan. A spokeswoman from their London headquarters said:

ILD [interstitial lung disease] has been observed in patients, but causality hasn't been established. The problem with ILD is that it's a well-known phenomenon in patients that have advanced non-small cell lung cancer, and it is associated with other anticancer treatments such as chemotherapy and radiotherapy. We believe that the benefits of the drug far outweigh the potential risks.¹⁸

Independent view

The two independent drug bulletins in Japan—*The Informed Prescriber* and *Kusuri-no-Check*—have published widely on this issue and have helped to alert prescribers,

other health professionals and patients to the adverse drug-related effects that have occurred with gefitinib. Such information has not been forthcoming from the drug company.

Experience in other countries

A submission for approval of gefitinib in NSCLC is currently before the Food and Drug Administration (FDA) in the US.¹¹ In September 2002, the FDA's Oncologic Drugs Advisory Committee recommended accelerated approval of gefitinib based on IDEAL 1 and IDEAL 2 study results. However, FDA reviewers were concerned that there was no non-gefitinib-treated control group, that there were a number of patients with slowly growing, less aggressive cancers that made evaluation of results complicated, and that there were a number of other confounding factors. This concern was reinforced with the release of the INTACT 1 and INTACT 2 study results, which showed no survival benefit with gefitinib when used as first-line therapy in combination with standard chemotherapy regimens.¹⁹ It appears that the accelerated process has been put on hold and a decision from the FDA is not expected until May 2003.

Meanwhile, AstraZeneca announced in February 2003 that a Marketing Authorisation Application for gefitinib had been submitted in Europe for the treatment of locally advanced or metastatic NSCLC in patients who had failed prior chemotherapy.

Gefitinib has also been used for NSCLC in Western countries through expanded access programs, and has been trialled in patients with prostate, colorectal, breast, and head and neck cancers.¹

Risk factors

Various risk factors may contribute to the adverse reactions to gefitinib. Large interindividual variation in the metabolism of gefitinib may be one of the most important factors. But we believe another factor may be more important and this is related to the drug's mechanism of action.

Gefitinib inhibits the normal repair process when tissue is injured. Many patients received chemotherapy and/or radiation therapy before starting gefitinib and there may be residual tissue damage. Although this injury may be predictable, it is in precisely these patients that gefitinib has been used. In addition, infection may occur during the treatment course and the ensuing systemic inflammatory response syndrome may induce tissue injury in the lungs and various other organs. The process of repairing this injured lung tissue may be inhibited by gefitinib, with resulting pulmonary toxicity.

Extensive promotion and wide use of unapproved gefitinib

Use of unapproved gefitinib commenced in December 2000, when it was provided free of charge on a compassionate basis. Brief product information was provided.

The price in Japan is now ¥7216 (approximately US\$60, €56 or £38) per 250 mg tablet, or more than ¥210 000 (approximately US\$1800) for one month's treatment at a dose of 250 mg daily.

AstraZeneca has several websites including their own, www.astrazeneca.com, a site specifically devoted to gefitinib (Iressa), www.iressa.com, and one with information on EGFRs, www.egfr-info.com, which includes a special journal, *Signal*. These sites can be accessed by patients and their families and appear to us to give a false expectation about the safety and efficacy of the drug.

Conclusion

The regulation of information on websites is very difficult but premarketing promotion of unapproved drugs should be strictly controlled.

Expanded access programs, whereby new products are made available before approval on the grounds of compassionate use, are legal in the US and in European Union countries. However, it is very doubtful that prescribers and patients can access

sufficient information about unapproved drugs to make informed decisions about their use. Increased access to new products before approval is never ethical unless full information including animal toxicity studies and clinical trial results are disclosed. It is time to debate whether 'compassionate use' is ethical, even if full information is disclosed.

It is our opinion that the efficacy and safety of gefitinib and the regulatory approval process should be completely re-examined using data accumulated through clinical trials, expanded access programs and the postmarketing experience in Japan.

In the meantime gefitinib should be withdrawn, both in Japan and in Western countries where it is available through expanded access programs.

Further information about gefitinib and the experience in Japan can be obtained from the authors.

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