PH2162 Pharmacy Clerkship – Week 1 clinical rotation
Drug Monograph

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Prince of Wales Hospital
Drugs and Therapeutic Committee

Drug name: Gefitinib tablets (IRESSA™)250 mg

Requesting Unit: Department of Oncology

Supplier: Astrazeneca

Mechanism of Action: The mechanism of the clinical antitumor action of gefitinib is not fully characterized. Gefitinib inhibits the intracellular phosphorylation of numerous tyrosine kinases associated with transmembrane cell surface receptors, including the tyrosine kinases associated with the epidermal growth factor receptor (EGFR-TK). EGFR is expressed on the cell surface of many normal cells and cancer cells. No clinical studies have been performed that demonstrate a correlation between EGFR receptor expression and response to gefitinib.

Indication:
IRESSA is indicated as monotherapy for the continued treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies who are benefiting or have benefited from IRESSA.

Pharmacokinetics
Gefitinib is absorbed slowly after oral administration with mean bioavailability of 60%. Elimination is by metabolism (primarily CYP3A4) and excretion in feces. The elimination half-life is about 48 hours. Daily oral administration of gefitinib to cancer patients resulted in a 2-fold accumulation compared to single dose administration. Steady state plasma concentrations are achieved within 10 days.
Absorption and Distribution
Gefitinib is slowly absorbed, with peak plasma levels occurring 3-7 hours after dosing and mean oral bioavailability of 60%. Bioavailability is not significantly altered by food. Gefitinib is extensively distributed throughout the body with a mean steady state volume of distribution of 1400 L following intravenous administration. In vitro binding of gefitinib to human plasma proteins (serum albumin and α1-acid glycoprotein) is 90% and is independent of drug concentrations.

Metabolism and Elimination
Gefitinib undergoes extensive hepatic metabolism in humans, predominantly by CYP3A4. Three sites of biotransformation have been identified: metabolism of the N-propoxymorpholino-group, demethylation of the methoxy-substituent on the quinazoline, and oxidative defluorination of the halogenated phenyl group. Five metabolites were identified in human plasma. Only O-desmethyl gefitinib has exposure comparable to gefitinib. Although this metabolite has similar EGFR-TK activity to gefitinib in the isolated enzyme assay, it had only 1/14 of the potency of gefitinib in one of the cell-based assays. Gefitinib is cleared primarily by the liver, with total plasma clearance and elimination half-life values of 595 mL/min and 48 hours, respectively, after intravenous administration. Excretion is predominantly via the feces (86%), with renal elimination of drug and metabolites accounting for less than 4% of the administered dose.

Comparabile drugs available in HA formulary:
Cisplatin, carboplatin, paclitaxel (Taxol), docetaxel (Taxotere), topotecan, irinotecan, vinorelbine, gemcitabine

<table>
<thead>
<tr>
<th>Product name</th>
<th>Active ingredient</th>
<th>Manufacturer</th>
<th>Cost</th>
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<tr>
<td>Cisplatin-Aq 1 mg/mL Vial</td>
<td>cisplatin</td>
<td>Sicor Pharm</td>
<td>$127.98 per 50milliliters</td>
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<td>Sicor Pharm.</td>
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<td>Carboplatin</td>
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<td>Sicor Pharm.</td>
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<td>Taxol 30 mg/5 mL Vial</td>
<td>Paclitaxel</td>
<td>Bms Onco/Immun</td>
<td>$175.35 per 5milliliters</td>
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<td>Taxotere 20 mg/0.5 mL Vial</td>
<td>Docetaxel</td>
<td>Aventis Pharm</td>
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<td>Topotecan</td>
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<td>Pharmacia/Upjohn</td>
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<td>Gemcitabine</td>
<td>Eli Lilly &amp; Co.</td>
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<td>Iressa 250 mg Tablet</td>
<td>Gefitinib</td>
<td>Astrazeneca</td>
<td>$2127.35 per 30each</td>
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</tbody>
</table>
Efficacy:

Efficacy and History

- In the IDEAL 1 trial, the tumor response was similar between previously-treated patients who received gefitinib 250 mg/day (18.4%) and 500 mg/day (19%).
- Preliminary analysis of the IMPACT 1 and 2 trials has shown that the addition of gefitinib to standard combination chemotherapy (i.e., gemcitabine/cisplatin or paclitaxel/carboplatin) in chemotherapy-naive patients did not offer a survival advantage.
- Preclinical trials have demonstrated additive or synergistic effects when gefitinib was added to chemotherapy and radiation therapy.
- The inhibition of EGFR occurs at gefitinib concentrations readily achievable with oral dosing (50% inhibitory concentration range 0.02—0.08 μmol/L).
- In September 2002, the FDA Oncology Drug Advisory Committee recommended approval of gefitinib for the treatment of advanced non-small cell lung cancer as third line therapy (i.e., following administration of at least 2 other chemotherapy regimens).
- On May 5, 2003, the FDA approved gefitinib for the treatment of locally-advanced or metastatic NSCLC in patients who have failed both platinum-based and docetaxel-based therapies.
- On June 17, 2005, due to an absence of a survival benefit, the indication for gefitinib was modified to only include patients who either benefited from current or past gefitinib.
  - The FDA large clinical trial comparing gefitinib with placebo in patients (n=1700) with refractory NSCLC showed no survival benefit from taking gefitinib.
  - The National Cancer Institute halted a randomized, placebo-controlled clinical trial (S0023) in patients (n = 672) with advanced NSCLC following chemotherapy and radiation based upon interim analysis evaluation that indicated a lack of survival improvement in the gefitinib arm.

Gefitinib is slowly absorbed, with peak plasma levels occurring 3-7 hours after dosing and mean oral bioavailability of 60%. Bioavailability is not significantly altered by food. Gefitinib is extensively distributed throughout the body with a mean steady state volume of distribution of 1400 L following intravenous administration. In vitro binding of gefitinib to human plasma proteins (serum albumin and α1-acid glycoprotein) is 90% and is independent of drug concentrations.

In human liver microsome studies, gefitinib had no inhibitory effect on CYP1A2, CYP2C9, and CYP3A4 activities at concentrations ranging from 2-5000 ng/mL. At the highest concentration studied (5000 ng/mL), gefitinib inhibited CYP2C19 by 24% and CYP2D6 by 43%. Exposure to metoprolol, a substrate of CYP2D6, was increased by 30% when it was given in combination with gefitinib (500 mg daily for 28 days) in patients with solid tumors.

Growth Factor Receptor Tyrosine Kinase, in Symptomatic Patients With Non–Small Cell Lung Cancer: A Randomized Trial.

There is no comparable prospective series treating a cohort of symptomatic patients who had received both cisplatin or carboplatin and docetaxel. In a retrospective review of 43 individuals treated with various chemotherapies, the response rate for a third regimen was 2%. One study randomized individuals who had received 1 or more chemotherapy regimen(s) to either docetaxel or supportive care alone. The response rate with docetaxel was 6%. Those who did not receive chemotherapy had a median survival of 5 months.

In another “second-line” trial conducted in the United States, radiographic tumor regressions were induced in 7% of patients receiving docetaxel vs in 1% of those receiving vinorelbine or ifosfamide. The 10% response rate with gefitinib (Iressa), achieved without myelosuppression or neurotoxicity, and with virtually no hair loss, is provocative in comparison. The results of this trial are consistent with the gefitinib phase 1 experience in patients with NSCLC. The recent international phase 2 trial (IDEAL1) also compared 250-mg and 500-mg gefitinib doses, but in patients pretreated with 1 or 2 prior chemotherapy regimens who were not required to have symptoms at trial entry. For the 250-mg dose, they reported an 18% radiographic response rate. Similar efficacy has been observed with the EGFR tyrosine kinase inhibitor erlotinib (OSI-774, Tarceva, OSI Pharmaceuticals, Melville, NY). In our study, approximately 15% of patients with the “best response” of progression had some symptomatic improvement by study criteria. This likely reflects either a placebo effect or the resolution of adverse effects of the prior chemotherapy regimens.

There is a about FDA drug approval summary: gefitinib (ZD1839) (Iressa) tablets By Division of Oncology Drug Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration.

On May 5, 2003, gefitinib (Iressa), ZD1839) 250-mg tablets received accelerated approval by the U.S. Food and Drug Administration as monotherapy treatment for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of both platinum-based and docetaxel chemotherapies. Information provided in this summary includes efficacy and safety results of relevant clinical trials. Effectiveness was demonstrated in a randomized, double-blind, phase II, multicenter trial comparing two oral doses of gefitinib (250 mg/day versus 500 mg/day). Two hundred sixteen patients were enrolled. The 142 patients who were refractory to or intolerant of a platinum and docetaxel comprised the evaluable population for the efficacy analysis. A partial tumor response occurred in 14% (9 of 66) of patients receiving gefitinib 250 mg/day and in 8% (6 of 76) of patients receiving gefitinib 500 mg/day. The overall objective response rate for both doses combined was 10.6% (15 of 142 patients) (95% confidence interval 6.0%-16.8%). Responses were more frequent in females and in nonsmokers. The median duration of response was 7.0 months (range 4.6-18.6+ months). Other submitted data included the results of two large trials conducted in chemotherapy-naive, stage III and IV NSCLC patients. Patients were randomized to receive gefitinib (250 mg or 500 mg daily) or placebo, in combination with either gemcitabine plus...
cisplatin (n = 1,093) or carboplatin plus paclitaxel (n = 1,037). Results from those studies showed no benefit (response rate, time to progression, or survival) from adding gefitinib to chemotherapy. Consequently, gefitinib is only recommended for use as monotherapy. Common adverse events associated with gefitinib treatment included diarrhea, rash, acne, dry skin, nausea, and vomiting. Most toxicities were Common Toxicity Criteria grade 1 or 2. Interstitial lung disease (ILD) has been observed in patients receiving gefitinib. Worldwide, the incidence of ILD is about 1% (2% in the Japanese postmarketing experience and about 0.3% in a U.S. expanded access program). Approximately one-third of the cases were fatal. Physicians should promptly evaluate new or worsening pulmonary symptoms. If ILD is confirmed, appropriate management includes discontinuation of gefitinib. Gefitinib was approved under accelerated approval regulations on the basis of a surrogate end point response rate. No controlled gefitinib trials, to date, demonstrate a clinical benefit, such as improvement in disease-related symptoms or greater survival. Accelerated approval regulations require the sponsor to conduct further studies to verify that gefitinib therapy produces such a benefit.

**Different response rates of drugs for NSCLC**

**Gefitinib (Iressa):**
14% (9 of 66) of patients receiving gefitinib 250 mg/day and in 8% (6 of 76) of patients receiving gefitinib 500 mg/day. The overall objective response rate for both doses combined was 10.6% (15 of 142 patients) (95% confidence interval 6.0%-16.8%). Responses were more frequent in females and in nonsmokers. The median duration of response was 7.0 months

**Gemcitabine:**
Gemcitabine in NSCLC has been evaluated extensively. Eight trials evaluated single agent; the response rate was 19-25% with median survival of 6.4 ? 9.4 months and 35-44% one year survival. When continued with Cisplatin, the response rate improved to 38-42% with median survival of 33-60 months and 1 year survival of 40-60%. Gemcitabine-Cisplatin combination had significantly better response rate and median survival when compared with other Cisplatin based therapies. These studies suggested that Cisplatin-Gemcitabine combination can be considered as standard therapy in NSCLC

**Taxol:**
Single agent Docetaxel showed response rate of 29% in pooled six trials and individual response rate ranging between 21-38% which was significantly higher than conventional therapy. Docetaxel-Cisplatin combination had response rate and median survival comparable to Docetaxel alone. Use of Docetaxel as a second line drug showed response rate of 16-21% and median and 1 year survival better than best supportive care. Docetaxel is also shown to have good response as adjuvant therapy in post radiotherapy and post surgery patients.

**Vinorelbine:**
Vinorelbine has a response rate of 12-14% in NSCLC as a single agent. It is also being evaluated as second line agent in NSCLC.
Safety:

Side effects
Side effects that are very common: (more than 10 of every 100 patients are likely to have them):
- Diarrhoea
- Nausea (feeling sick)
- Skin reactions such as acne-like rash, sometimes itchy with dry skin

Side effects that are common: (1 to 10 of every 100 patients are likely to have them):
- Vomiting
- Loss of appetite
- Dehydration
- Red and sore mouth
- Nail problems
- Loss of hair
- Weakness
- Red and itchy eye
- Red and sore eyelid
- Nose bleed and blood in the urine

Side effects that are rare (less than 1 in every 1000 patients is likely to have them):
Inflammation of the pancreas, with symptoms such as very severe pain in the upper part of the stomach area and severe nausea (feeling sick) and vomiting

Side effects that are very rare (less than 1 in every 10000 patients is likely to have them):
Allergic reactions, including swelling of lips and hives or nettle-rash

Contact physician without delay if any of the following happens:
- Serious breathlessness, or sudden worsening breathlessness, possibly with a cough or fever. Some patients taking IRESSA get an inflammation of the lungs called interstitial lung disease. This side effect is uncommon (less than 1 in every 100 patients), and some of the patients have died from this.
- Persistent or severe diarrhoea, vomiting, nausea (feeling sick) or loss of appetite. Some patients have suffered from dehydration following these side effects.
- New eye problems, such as pain, redness or change in vision. Some patients have suffered from ulcer on the surface of the eye (cornea), sometimes with ingrowing eyelashes.
- Severe skin reactions affecting large portions of your body including redness, pain, ulcers, blisters, skin sloughing or involvement of lips and mucous membranes (toxic epidermal necrolysis, erythema multiforme). This type of skin reaction is very rare (less than 1 in every 10000 patients is likely to have them).
**Precautions**

**Hepatotoxicity**
Asymptomatic increases in liver transaminases have been observed in IRESSA treated patients; therefore, periodic liver function (transaminases, bilirubin, and alkaline phosphatase) testing should be considered. Discontinuation of IRESSA should be considered if changes are severe.

**Hepatic Impairment**
Gefitinib is cleared primarily by the liver. Therefore, gefitinib exposure may be increased in patients with hepatic dysfunction. In patients with liver metastases and moderately to severely elevated biochemical liver abnormalities, gefitinib pharmacokinetics was similar to the pharmacokinetics of individuals without liver abnormalities. The influence of non-cancer related hepatic impairment on the pharmacokinetics of gefitinib has not been evaluated.

**Patients’ information**
Patients should be advised to seek medical advice promptly if they develop severe or persistent diarrhea, nausea, anorexia or vomiting, an onset or worsening of pulmonary symptoms (shortness of breath or cough), an eye irritation or any other new symptoms.

Women of childbearing potential must be advised to avoid becoming pregnant.

**Clinical evidence**
From Giaccone’s study[1], common adverse events associated with gefitinib treatment included diarrhea, rash, acne, dry skin, nausea, and vomiting. Interstitial lung disease has been observed in patients receiving gefitinib. Worldwide, the incidence of interstitial lung disease was about 1% (2% in the Japanese post-marketing experience and about 0.3% in a United States expanded access program).

From Herbst’s study [2], Expected dose-related diarrhea and skin toxicity were observed in gefitinib-treated patients, with no new significant/unexpected safety findings from combination with chemotherapy


**Contraindications:**
Hypersensitivity to gefitinib or any component of the formulation; pregnancy.

**Interaction with other medicinal products and other forms of interaction:**
Metabolism of gefitinib is predominantly via CYP 3A4 as shown by in vitro studies.
Gefitinib plasma concentrations may be decreased by substances which are inducers of CYP3A4; the enzyme activity may increased and metabolism of gefitinib is increased. Therefore, co-medication with CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, barbiturates or St John’s Wort) may reduce efficacy. In healthy volunteers co-administration with rifampicin (a known potent CYP34 inducer) reduced mean gefitinib AUC by 83% of that without rifampin.

There is an 80% increase in the mean AUC of genfitinib when co-administered with itraconazole (a CYP3A4 inhibitor) in healthy volunteers. This increase may be clinically relevant since adverse experiences are related to dose and exposure.

It results in a reduced mean gefitinib AUC by 47% when co-administration with drugs that cause significant sustained elevations in gastric pH ≥5.

Increases in bleeding events have been observed in cancer patients taking warfarin and IRESSA.