National PBM Drug Monograph
Gefitinib (Iressa™)
July 2003
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

Introduction[1,2]

The majority of patients with non-small cell lung cancer (NSCLC) are diagnosed with advanced disease or develop metastases following initial therapy. Platinum-based chemotherapy regimens have prolonged median and 1-year survival rates when used as first-line therapy in advanced disease. More recently, taxanes in combination with platinum or another active drug have shown good results in first and second-line therapies. Docetaxel as a single agent has been approved for second-line therapy. There is currently no effective therapy for patients who have failed platinum based and a taxane chemotherapy regimen.

The epidermal growth factor receptor (EGFR) is a member of the HER family of transmembrane glycoproteins that possess tyrosine kinase activity, and is present in nearly all NSCLC specimens and over-expressed in some specimens. Gefitinib is a small molecule compound that binds to ATP sites on tyrosine kinase, blocking signal transduction. Gefitinib was approved in May 2003 as monotherapy for patients with locally advanced or metastatic NSCLC who have failed on both platinum based and docetaxel based chemotherapy regimens.

Pharmacology/Pharmacokinetics[2,3]

Gefitinib is a small molecule quinazoline that inhibits the activity of EGFR by binding to ATP sites on the intracellular tyrosine kinase domain of the receptor. Binding to the ATP sites inhibits autophosphorylation of EGFR and blocks downstream signaling. Activation of downstream receptor signaling generally results in increased angiogenesis, increased cell proliferation, decreased apoptosis, and increased invasion and metastatic potential. The antitumor action of gefitinib has not been fully characterized. Data correlating EGFR expression and response to gefitinib are inconclusive.

Table 1. Pharmacokinetic Parameters

Parameter	Results	Comments
Absorption	Bioavailability 60% T_{max} 3-7 hours	Bioavailability not significantly altered by food
Distribution	Vd_{ss} 1400 L 90% plasma protein binding	
Metabolism	Hepatic, primarily CYP3A4	At concentrations of 2-5000 ng/ml, did not inhibit CYP1A2, CYP2C9, CYP3A4; at 5000ng/ml inhibited CYP2C19 by 24% and CYP2D6 by 43%. At doses of 500mg/d, caused a 30% increase in metoprolol levels; metoprolol is a substrate of 2D6
Elimination	Terminal $t_{1/2}$ = 48 hours (37-65) Excretion 1° feces (86%) Renal elimination <4%	

FDA Approved Indication(s) and Off-label Uses

Gefitinib is indicated as monotherapy in locally advanced or metastatic non-small cell lung cancer in patients who have failed both a platinum based and a docetaxel chemotherapy regimen.

Two trials were conducted in chemotherapy naïve patients with stage II and IV non-small cell lung cancer (INTACT 1 and INTACT 2) comparing the addition of gefitinib 250mg, 500mg or placebo to two different platinum-based chemotherapy regimens. In these trials the addition of gefitinib did not increase the response rates, time to progression, or overall survival and should not be used in combination with chemotherapy for first line therapy.

Dosage and Administration

The daily dose of gefitinib is one 250mg tablet with or without food. Higher doses did not yield better responses.

No dose adjustment is needed because of age, gender, body weight, ethnicity, renal function, or moderate to severe hepatic impairment.

Dose Adjustments

1. Poorly tolerated **diarrhea** (with or without dehydration): Hold dose for up to 14 days, then reinstate at 250mg per day.

2. **Skin** adverse reactions: Hold dose for up to 14 days, then reinstate at 250mg per day.

3. Acute onset or worsening **pulmonary symptoms** (dyspnea, cough, fever): Hold dose and investigate symptoms. If interstitial lung disease is confirmed, discontinue gefitinib and initiate appropriate therapy.

4. If new **eye symptoms** develop, such as pain, evaluate and manage appropriately including interruption of gefitinib therapy and removal of abnormal eyelashes. Once symptoms resolve, consider restarting gefitinib.

5. If receiving **potent CYP3A4 inducers** (rifampicin or phenytoin) consider increasing dose to 500mg per day in the absence of severe adverse reactions.

Adverse Effects (Safety Data)

Table 2. Drug Related Adverse Events in ≥5% at 250mg dose in registration trial

	% of Patients				
Adverse Event	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	48	41	6	1	0
Rash	43	39	4	0	0
Acne	25	19	6	0	0
Dry skin	13	12	1	0	0
Nausea	13	7	5	1	0
Vomiting	12	9	2	1	0
Pruritus	8	7	1	0	0
Anorexia	7	3	4	0	0
Asthenia	6	2	2	1	1

Other (All Grades):

Peripheral Edema	2%	Vesiculobullous rash	1%
Amblyopia	2%	Mouth ulceration	1%
Dyspnea	2%		
Conjunctivitis	1%		
Interstitial Lung Disease:	1%		

Precautions/Contraindications

Contraindications:
Gefitinib is contraindicated in patients with severe hypersensitivity to the parent drug or any of its components.

Precautions:

Hepatotoxicity – Asymptomatic increases in transaminases have occurred in clinical trials. Patients with liver metastases and moderate to severely elevated transaminases did not have significant changes in gefitinib pharmacokinetics. Periodic liver function tests (transaminases, bilirubin, and alkaline phosphatase) are recommended. Consider discontinuation of gefitinib if changes are severe.

Drug Interactions – Potent inducers of CYP3A4 (e.g. rifampin and phenytoin) increase the metabolism of gefitinib and decrease plasma levels. Consider increasing the dose to 500mg per day in the absence of severe adverse reactions. Potent inhibitors of CYP3A4 (ketoconazole and itraconazole) decrease the metabolism and increase plasma gefitinib levels. This may result in increased adverse events and caution is recommended when administering inhibitors with gefitinib.

Warfarin – Increases in INR and/or bleeding have been reported in patients on warfarin and gefitinib. Regular monitoring of INR is recommended for patients taking both drugs.

Carcinogenesis, Mutagenesis – Testing for genotoxicity in *in vitro* assays and *in vivo* animal systems did not produce genetic damage. Testing for carcinogenicity has not been conducted.

Any drug that decreases gastric pH (histamine-2 antagonist, sodium bicarbonate) may decrease plasma concentrations and may reduce efficacy.

Geriatric Use: In clinical trials, no differences in safety and efficacy were observed for the 30.5% of patients 65 – 74 years old and the 5% of patients >75 years old when compared to younger patients.

Pulmonary toxicity: Interstitial Lung Disease (ILD) has been observed in 1% of patients on gefitinib; 1/3 of cases have been fatal. The incidence is approximately 2% in Japan, 0.3% in the expanded access program in the USA, and 1% in the first-line trials in the USA for NSCLC (the incidence was the same in the placebo group). ILD has been reported as interstitial pneumonia, pneumonitis, and alveolitis and presents as an acute onset of dyspnea, sometimes with cough or low-grade fever, becoming severe in a short period of time and requires hospitalization and treatment with systemic steroids.[4]

Ocular toxicity: Corneal irritation and pain due to aberrant eyelash growth has been reported, especially during phase 1 dose-escalation studies.

Drug Interactions

Metoprolol: Gefitinib inhibits CYP2D6 by <50% in vitro. In a phase I trial, gefitinib increased the serum levels of metoprolol, a CYP2D6 substrate, by 30%. There was no evidence this was clinically significant.

Itraconazole: Co-administration of gefitinib and itraconazole, a potent CYP3A4 inhibitor, increases exposure to gefitinib.

Rifampin: Co-administration of gefitinib and rifampin, a potent inducer of CYP3A4, decreases exposure to gefitinib.

Ranitidine/sodium bicarbonate: In healthy volunteers, sustained elevation of gastric pH >5.0 resulted in a reduction of the mean AUC.

Warfarin: Increased INR readings and bleeding episodes have been observed in patients taking warfarin concomitantly with gefitinib. It is recommended that patients taking warfarin while on gefitinib should be monitored regularly for INR changes and bleeding.

Efficacy Measures

Primary Objectives in registration trial:
1. Tumor response
2. Disease-related symptom improvement rate
3. Safety profile

Secondary Objectives:
1. Disease control rates (responses + stable disease)
2. Progression-free survival
3. Overall survival
4. Time to worsening of symptoms
5. Changes in QoL

Clinical Trials

Table 3. Registration Trial- Monotherapy in Third-Line Treatment Setting[5]

Outcome	Gefitinib 250mg (N=102)	Gefitinib 500mg (N=114)
Objective Response	11.8%	8.8%
Symptom improvement	43.1%	35.1%
Progression-free survival (median)	59 days	60 days
Median survival	185 days	183 days
Disease Control	42.2%	36%

Entry requirements:
- Patients with locally advanced or metastatic non-small cell lung cancer that had received treatment with at least 2 chemotherapy regimens that were platinum- and docetaxel-based (need not be given concurrently).
- Failures of previous chemotherapy regimens were the result of disease progression during or within 90 days of the last dose of chemotherapy or treatment intolerance.
- Required to have symptomatic disease as evidenced by a score of ≤24 on the Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L) instrument (a score of 28 on the LCS indicates no symptoms).
- By FDA analysis, 139/216 patients (64%) met the eligibility criterion. Seventy-seven patients were not refractory or intolerant to docetaxel, platinum, or both drugs.

Response:
- 22/216 patients had a partial response for a response rate of 10.2% (95% CI 6.5,15). In 18 patients the response was documented by measurable disease while 4 patients had a PR with non-measurable disease. 61% of patients received 3 or more previous chemotherapy regimens.
- Disease Control-This was determined to not be meaningful because the majority of patients had slow growing tumors (adenocarcinoma histology).
- The majority of patients (72.7%) had an objective response by the third or fourth week; objective responses were seen as late as week 16 of therapy (2 patients).
- Disease related symptom improvement is defined as a sustained 2-point improvement on the LCS for at least 4 weeks without an interim worsening.
- Baseline median LCS score was 16. In patients who had symptom improvement, the median increase in LCS score was 7 points.
- Symptom response correlated with disease response; patients with objective responses had the highest symptom response, followed by stable disease, and then progressive disease. Patients experiencing symptom response also had a longer overall survival.[6]

- FDA believes that symptom improvement without a concurrent, randomized control arm and no prospective plan for collecting data on use of supportive care agents (e.g., oxygen and opiates) is not a reliable measure.
- Patient characteristics associated with variable response rates: women responded better than men (17.5% vs. 5.1%), nonsmokers responded better than current or previous smokers (29.4% vs. 4.6%), and adenocarcinoma histology responded better than other histologies (12.4% vs. 6.7%).

Adverse Events:

- Fewer patients on the 250mg/day dose experienced Grade 3 or 4 drug-related adverse events (6.9% vs. 17.5%)
- Fewer patients on the 250mg/day dose withdrew because of drug-related adverse events.
- There were fewer interruptions of drug therapy due to adverse events in the 250mg/day dose group.
- Dose reductions due to toxicity occurred in 1% of the 250mg/day patients and 8.8% of the 500mg/day patients.
- There were no deaths due to drug-related adverse events in the 250mg/day dose group, and 1 death due to drug-related adverse events in the 500mg/day dose group.

Table 4. Supporting Data- Monotherapy in advanced NSCLC who previously received a least one chemotherapy regimen with platinum (Japanese and non-Japanese patients)[7]

Outcome	**Gefitinib 250mg (N=103)**	**Gefitinib 500mg (N=106)**
Objective Response	18.4%	19%
Symptom improvement	40.3%	37%
Progression-free survival (median)	83 days	85 days
Median survival	Not yet reached at 4 months of follow-up	Not yet reached at 4 months of follow-up
Disease Control	54.4%	51.4%

Entry requirements:

- Patients with locally advanced or metastatic non-small cell lung cancer that had recurrent or refractory disease following one or a maximum of two chemotherapy regimens that included platinum.
- Disease specific symptoms were NOT a requirement for study entry.

Response:

- 38/208 patients had objective responses (1 CR + 37 PR) for a response rate of 18.8%.
- There was no difference in response between patients who had received 1 or 2 previous chemotherapy regimens.
- Women responded better than men, adenocarcinoma histology responded better, and Japanese patients responded better than white (25.9% vs. 11%).
- FDA analysis concluded that only 35% of patients in this study were chemotherapy resistant having progressed on first or second-line therapy.

Other:

Table 5. Phase II trial in recurrent or metastatic squamous cell carcinoma of the head and neck[8]

Outcome	**Gefitinib 500mg/day (N=47)**
Objective Response	10.6% (95% CI 3.5,23.1) (1 CR+4PR)
Stable Disease	42.6%
Disease Control (CR+PR+SD)	53%
Median Time To Progression	3.4 months
Median Overall Survival	8.1 months

Entry requirements:

- Recurrent or metastatic SCCHN who were ineligible for curative surgery or radiotherapy
- No more than one previous systemic therapy for incurable, recurrent, or metastatic disease
- No chemotherapy or radiotherapy within 4 weeks of study entry

Adverse Events:

- The most common adverse events were dermatologic and gastrointestinal.
- Dermatologic adverse events included acneform rash, brittle hair, and onycholysis
- The most common GI adverse event was diarrhea that required dose reduction in four patients.
- 20% experienced hypercalcemia without evidence of bone disease; the finding preceded radiographic evidence of non-skeletal disease progression in all but 1 patient

Factors related to response, progression, and survival:

- Factors associated with disease control are performance status and the development of skin toxicity
- Factors associated with increased TTP included performance status, skin toxicity; metastatic disease negatively affected TTP compared to those with recurrent disease
- Factors associated with increased survival included performance status, achieving an objective response, disease control, and skin toxicity.
- Immunohistochemical staining for EGFR, extracellular signal-related kinase, and phosphorylated extracellular signal-related kinase before and after treatment found no correlation between response and staining for any of the proteins.

Acquisition Costs

Drug	Dose	Cost/Day/patient ($)	Cost/Month/patient ($)
Gefitinib	250mg tablet	38.92	1167.70

In the registration trial 67% of patients received gefitinib for ≤ 3 months.

Conclusions

Efficacy

In phase I trials, gefitinib has been studied in a variety of solid tumors including non-small cell lung cancer. It has been shown to be safe and tolerable over a range of doses. Dose limiting toxicity (diarrhea) was seen at doses >600mg/day. Pharmacodynamic assessment of EGFR in skin samples taken after therapy found that EGFR expression did not change, activated EGFR was decreased, and most significant were changes in downstream signaling pathways, e.g. reduction of MAPK and increases in the cyclin-dependent inhibitor $p27^{K1P-1}$. These changes occurred over the entire range of doses studied. Objective responses were seen at all dose levels.[9,10] For phase II studies 250mg and 500mg/day were chosen to minimize toxicity.

Phase II results in patients who have failed at least two prior chemotherapy regimens including a platinum-based and docetaxel based regimen produced objective responses and disease-related symptom improvement, however there was no comparison arm and therapy for symptom management (oxygen and opiates) was not controlled for prospectively.

Despite promising results in a pilot study that added gefitinib to first-line chemotherapy in NSCLC, two large randomized, placebo controlled trials failed to show any benefit from the addition of gefitinib to first-line chemotherapy.[11]

Safety

In phase I and II studies, gefitinib was well tolerated with predictable and reversible toxicities. The most common drug-related toxicities were grade 1/2 skin changes (acneform rash, dry skin, pruritus) and grade 1/2 gastrointestinal effects (diarrhea, nausea, vomiting). There is no evidence of cumulative toxicity. Grade 3 drug-related adverse events occurred in 4.9% of patients at the 250mg/day dose level. Grade 4 drug-related adverse events occurred in 2%.

Toxicities with a low incidence that may cause concern are elevations of AST/ALT and interstitial lung disease. Interstitial lung disease was fatal in 1/3 of patients. However, ILD is not uncommon in NSCLC and has occurred following radiation therapy, chemotherapy, and chemoradiotherapy combination therapy in NSCLC patients who have inoperable locally advanced disease.[12,13,14,15,16]

Recommendations

Table 6. Overview of Therapy for Advanced Non-small Cell Lung Cancer

	Objective Response	Median Survival	Reduction in Risk of Death
First-line Therapy Cochrane Review[17] (cisplatin based regimens versus best supportive care)		5.5 months (increased survival at 1 year from 15% to 25%)	27%
ECOG[18] (comparison of 3 cisplatin/carboplatin regimens to cisplatin/paclitaxel)	19%	8 months (survival of 34% at 1 year)	
MD Anderson[19] (retrospective analysis of patients receiving at least 3rd line chemotherapy)	20.9%	15.7 months	
Second-line Therapy Docetaxel vs best supp. care[20]	7.1%	7.5 months (survival of 37% at 1 year)	
MD Anderson	16.3%	9.8 months	
Third or Fourth-line Therapy MD Anderson	2.3%	5.4 months	

Despite the addition of new chemotherapy agents, such as the taxanes, gemcitabine, and the topoisomerase I inhibitors, to platinum-based regimens response rates to chemotherapy in advanced non-small cell lung cancer patients have only marginally improved. Survival also remains stagnant at 8-10 months. Treatment with chemotherapy regimens as third+-line therapy is untested and produces poor results. Third-line therapy is an unmet need.

Gefitinib, administered orally, is a selective and reversible inhibitor of EGFR that binds to ATP and prevents autophosphorylation and kinase activation. This results in inhibition of proliferation and angiogenesis, and induction of apoptosis. In phase II clinical trials, there was no difference in efficacy between the 250mg and the 500mg dose, but the 500mg dose produced more adverse events and should not be used unless the patient in on a potent inducer of CYP3A4. Although the response rate in the phase II trial for third line therapy was relatively low, objective responses were accompanied by disease-related symptom improvement. Whether that improvement in symptoms was totally due to gefitinib or to the combination of gefitinib and symptom management with oxygen and opiates is unknown. Of interest is the fact that symptom scores did not improve as much in patients who did not have an objective response. Gefitinib is also generally well tolerated, with skin and GI toxicities predominating at the 250mg/ day dose.

Areas of uncertainty include: the failure of gefitinib to improve results when added to chemotherapy in the first-line setting, the lack of a measurable target (gefitinib is effective in tumors with a wide range of EGFR expression), the variability of pharmacodynamic activity of EGFR in skin samples after therapy as a way to predict outcomes in tumors[21], the lower response rate in men and current or past smokers, and the lack of a comparison arm with regard to symptom improvement and survival.

Gefitinib meets an unmet need in the treatment of non-small cell lung cancer in patients who are symptomatic and have progressed or are intolerable to two previous chemotherapy regimens including a platinum- and docetaxel-based regimen. It should be made available to this population as an alternative to or addition to best supportive care.

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