Summary

✓ Gefitinib is approved as monotherapy for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in patients who have failed prior platinum-based treatment and docetaxel chemotherapy.¹

✓ Its efficacy when compared to standard treatment and best supportive care is unproven.

✓ Common drug-related adverse effects include gastrointestinal and skin disorders.

✓ Rare but serious drug-related adverse events, such as shock, thrombophlebitis, thrombocytopenia and interstitial lung disease, have been reported.

Patient Group

Approximately 21,100 Canadians were diagnosed with lung cancer in 2003.⁶ NSCLC accounts for 80% to 85% of all lung cancers, implying that approximately 18,000 patients may have developed NSCLC in 2003.⁷ The overall five-year survival rate of patients with NSCLC is 15%.⁸

Most patients have locally advanced disease (stage III) or distant metastases (stage IV) at the time of diagnosis.⁹,¹⁰ Untreated stage IV patients have a median survival of four to five months and a one-year survival rate of 10%.¹²

Current Practice

Medically suitable patients with inoperable stage III NSCLC are generally offered radiotherapy with concurrent chemotherapy. Stage IV patients are offered chemotherapy alone. Some may require palliative radiotherapy. First-line chemotherapeutic regimens include platinum-based agents (cisplatin or carboplatin) combined with vinorelbine, gemcitabine, docetaxel or paclitaxel.¹¹,¹³ A recent randomized study comparing four platinum-based doublets in untreated stage IIIB or stage IV NSCLC patients showed an overall response rate of 19%, a median survival of 7.9 months and a one-year survival rate of 33%.¹² Docetaxel is generally used after the failure of platinum-based chemotherapy. The median survival time for patients using it as second-line treatment is 7.5 months and the one-year survival rate is 37%.¹⁴ After the failure of first- and second-line treatments, patients are offered best supportive care.
The Evidence

The Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) 1 and IDEAL 2 trials were conducted in patients with advanced NSCLC. Patients were randomized to 250 mg or 500 mg gefitinib tablets daily until disease progression or interruption of treatment due to toxicity.

Patients were eligible if they had recurrent or refractory disease with one or two chemotherapy regimens (including one containing platinum therapy) in IDEAL 1. In IDEAL 2, patients were included if they had developed toxicity or progressed with two or more regimens containing a platinum agent and docetaxel. In both trials, however, inclusion criteria were not followed. Many participants had responded or had not progressed with prior treatment. The response to gefitinib was unrelated to prior treatment response.

Symptom improvement response rates ranged from 35% to 43%. These results may not be meaningful given that there was no comparator regimen and patients used concomitant medications that may have contributed to symptom relief.

The Iressa NSCLC Trial Assessing Combination Treatment (INTACT) 1 and INTACT 2 trials were conducted in chemo-naïve patients with advanced NSCLC receiving first-line therapy with gemcitabine-cisplatin or paclitaxel-carboplatin with or without gefitinib. There were no statistically significant differences between the treatment arms for overall survival, progression-free survival and time to worsening of symptoms.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Previous Treatment History</th>
<th>Primary End Points Results</th>
<th>Secondary End Points Results</th>
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<tbody>
<tr>
<td>IDEAL 1</td>
<td>(n=210)</td>
<td>70.5% males, 80.5% stage IV NSCLC, 62.9% adenocarcinoma, 69.0% performance status=1</td>
<td>†objective tumour response rates 18.4% (250 mg), 18.9% (500 mg); objective tumour response rate in Caucasians 10.8%</td>
<td>median progression-free survival 83 days (250 mg), 85 days (500 mg); median overall survival 7.6 months (250 mg), 8.0 months (500 mg)</td>
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<td>26.3% progression on first-line chemotherapy, 34.9% progression on first- or second-line chemotherapy</td>
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<tr>
<td>IDEAL 2</td>
<td>(n=216)</td>
<td>56.9% males, 88.9% stage IV NSCLC, 66.2% adenocarcinoma, 64.4% performance status=1</td>
<td>§objective tumour response rates 11.8% (250 mg), 8.8% (500 mg); overall objective tumour response rate 10.2%; objective tumour response rate in eligible patients 10.1%</td>
<td>median progression-free survival 59 days (250 mg), 60 days (500 mg); median overall survival 6.2 months (250 mg), 6.1 months (500 mg)</td>
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<td>64% refractory or intolerant to platinum and docetaxel</td>
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*no statistically significant differences between 250 mg and 500 mg groups
†includes complete response (n=1 in IDEAL 1), partial response (n=27 in IDEAL 1 and n=18 in IDEAL 2) and partial response in non-measurable but evaluable disease (n=1 in IDEAL 1 and n=4 in IDEAL 2)
§greater than 50% decrease in lesion size

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<tr>
<td>INTACT 1</td>
<td>6 cycles of gemcitabine 1,250 mg/m² on days 1 and 8 plus cisplatin 80 mg/m² on day 1 and placebo or gefitinib 250 mg or gefitinib 500 mg until disease progression</td>
<td>73.7% males, 69.2% stage IV NSCLC, 46.1% adenocarcinoma</td>
<td>median overall survival 10.9 months (chemotherapy + placebo), 9.9 months (chemotherapy + 250 mg), 9.9 months (chemotherapy + 500 mg)</td>
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<tr>
<td>INTACT 2</td>
<td>carboplatin and paclitaxel 225 mg/m² every 3 weeks for 6 cycles and placebo or gefitinib 250 mg or gefitinib 500 mg until disease progression</td>
<td>59.7% males, 80.4% stage IV NSCLC, 58.1% adenocarcinoma</td>
<td>median overall survival 9.9 months (chemotherapy + placebo), 9.8 months (chemotherapy + 250 mg), 8.7 months (chemotherapy + 500 mg)</td>
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*no statistically significant differences among all groups
Adverse Effects

Drug-related adverse events reported with the 250 mg dose in IDEAL 2 include gastrointestinal (40.8% diarrhea, 12.7% nausea and 11.8% vomiting) and skin disorders (43.1% rash, 24.5% acne, 7.8% pruritis and 12.7% dry skin). Rare (less than 1% but serious (grade 4) drug-related adverse events reported with the 250 mg or 500 mg dose include anemia, shock, pneumonia, thrombophlebitis, asthenia, thrombocytopenia, dehydration, lung hemorrhage, interstitial lung disease (ILD) and an increase in liver enzymes.15,17,19-21

ILD is a life-threatening condition that is observed in lung cancer patients. It is caused by their disease or by radiotherapy and chemotherapy.24,25 In Japan, where the drug has been approved for more than a year, the incidence of ILD with gefitinib is 2%, compared with 0.3% in the US, where 23,000 patients have been treated under the expanded-access program.5,26 ILD occurs earlier in Japanese patients treated with gefitinib (median time=24 days) than in American patients (42 days).18

Administration and Cost

A gefitinib 250 mg tablet is taken orally once daily. A 30-day supply costs $2,140 (Ms. Michele Eftoda, AstraZeneca, Mississauga, ON: personal communication, 2004 Jan 15). The treatment duration is undefined.

Concurrent Developments

The IRESSA Survival Evaluation in Lung Cancer trial is comparing gefitinib plus best supportive care versus placebo plus best supportive care in patients with advanced NSCLC.27 Gefitinib is being investigated in the treatment of other solid tumours in breast, prostate, kidney, ovary, head and neck, colorectal and brain cancers; in earlier stage lung cancer; in combination with irradiation and with other chemotherapy regimens.28,29

Other quinazolines in trials for the treatment of solid tumours include erlotinib (Tarceva® by Roche), canertinib (Pfizer) and lapatinib (GlaxoSmithKline).3,28

Rate of Technology Diffusion

The approval of gefitinib in Canada will significantly increase the cost of managing NSCLC. Of the 18,000 Canadians who get NSCLC this year, most will develop metastatic disease and 50% will be candidates for first-line chemotherapy. After disease progression, 30% will be candidates for second-line therapy, so approximately 1,000 Canadians could receive gefitinib as a third-line treatment option.

Implementation Issues

- Gefitinib has been given a conditional approval for use as third-line therapy, based on phase II trials, despite unproven benefits compared to best supportive care and incidence of serious adverse events.
- Results of the INTACT trials show that gefitinib does not improve median survival when used with standard chemotherapy regimens in chemo-naïve patients.
- There are no completed controlled trials of gefitinib as monotherapy in chemo-naïve or chemo-treated patients compared to placebo or other treatments.30,31

References


