Complete Summary

GUIDELINE TITLE

Use of the epidermal growth factor receptor inhibitors, gefitinib (Iressa®) and erlotinib (Tarceva®), in the treatment of non-small cell lung cancer: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Feld R, Sridhar SS, Shepherd FA, Mackay JA, Evans WK, Lung Cancer Disease Site Group. Use of epidermal growth factor receptor inhibitors, gefitinib (Iressa®) and erlotinib (Tarceva®), in the treatment of non-small cell lung cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Jan 6. 43 p. (Evidence-based series; no. 7-9). [88 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

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SCOPE

DISEASE/CONDITION(S)

Non-small cell lung cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the role of epidermal growth factor receptor (EGFR) inhibitors gefitinib (Iressa®) and erlotinib (Tarceva®) in the treatment of patients with advanced non-small cell lung cancer

Note: The focus of the practice guideline is on treatment for recurrent or relapsed disease, although evidence for the effectiveness of first-line treatment is reviewed where available. Most of the initial use for these compounds will be as second- or third-line treatment.

TARGET POPULATION

Adult patients with non-small cell lung cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Gefitinib monotherapy
2. Erlotinib monotherapy

Considered, but not recommended: gefitinib or erlotinib in combination with chemotherapy or as a maintenance therapy, gefitinib or erlotinib over docetaxel as routine second-line treatment.

MAJOR OUTCOMES CONSIDERED

Primary outcomes of interest

- Symptom control
- Quality of life
- Tumor response rate
- Survival

Secondary outcome of interest

- Toxicity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (1996 through November 2005), EMBASE (1996 through 2005, week 47), CANCERLIT (1975 through October 2002), and the Cochrane Library (2005, Issue 4) databases were searched. The subject headings "carcinoma, non-small-cell lung," "lung neoplasms," "lung non small cell cancer," "lung carcinogenesis," "lung adenocarcinoma," "lung alveolus cell carcinoma," "lung squamous cell carcinoma," "erlotinib," "gefitinib," and "epidermal growth factor receptor" were combined with each of the following phrases used as text words: "non small cell lung," "Iressa," "gefitinib," "ZD1839," "Tarceva," "erlotinib," "OSI774," and "EGFR-TK". These terms were then combined with the search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, clinical trials, phase II clinical trials, phase III clinical trials, and cohort analyses.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO) (1999-2005), the European Cancer Conference (ECCO) (1999-2003), the International Association for the Study of Lung Cancer (IASLC) (2003-2005) and the European Society for Medical Oncology (ESMO) (1999-2004) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov/) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

Study Selection Criteria

Inclusion Criteria

1. Practice guidelines on the use of gefitinib or erlotinib as treatment for non-small cell lung cancer (NSCLC); or
2. Meta-analyses or randomized trials (phase II or phase III) comparing gefitinib or erlotinib, alone or in combination with chemotherapy, to placebo, best supportive care (BSC), or chemotherapy, or comparing different doses or schedules of gefitinib or erlotinib; and
3. Fully published papers or published abstracts of trials that reported at least one of the following outcomes by treatment group: symptom control, quality of life (QOL), tumour response rate, or survival.

Exclusion Criteria

1. Pilot trials, dose-escalation trials, or case series (including expanded access programs) studies
2. Letters and editorials that reported clinical trial outcomes
3. Papers published in a language other than English, which were excluded because resource limitations do not allow for translation services

NUMBER OF SOURCE DOCUMENTS

Twelve randomized trials met the pre-defined eligibility criteria for this systematic review.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The data from the four first-line randomized phase III trials of chemotherapy with or without gefitinib or erlotinib were not pooled because the chemotherapy regimens used in the trials of each agent were different. The Lung Disease Site Group (DSG) will consider pooling the survival data of future fully published randomized trials of gefitinib or erlotinib if the comparison treatments are considered sufficiently homogenous to allow a meaningful evaluation.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Development and Internal Review

This evidence-based series was developed by the Lung Cancer Disease Site Group (DSG) of Cancer Care Ontario's Program in Evidence-based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on the use of epidermal growth factor receptor inhibitors, gefitinib (Iressa®) and erlotinib (Tarceva®), in the treatment of non-small cell lung cancer (NSCLC), developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

The systematic review on this topic is reported in Section 2 of the original guideline document and describes the body of relevant clinical evidence and the interpretation of this evidence by members of the DSG. The draft recommendations developed by the Lung DSG are summarized in Section 1 of the original guideline document. Erlotinib has been shown to improve survival compared with placebo in patients with relapsed or recurrent disease and is therefore recommended for use as a third-line therapy for patients who maintain good performance status after failing first- and second-line chemotherapy. Erlotinib is also an option for second-line therapy for patients who are not candidates for second-line chemotherapy. Members of the DSG suggested that circumstances in which patients would not be considered eligible for second-line chemotherapy include: patients with progression after first-line platinum-based and docetaxel chemotherapy, patients in whom first-line chemotherapy was discontinued (<4 cycles) due to poor tolerability, patients with borderline performance status and/or significant comorbidities that make them unlikely to tolerate 2nd-line chemotherapy, patients with medical contraindications from previous chemotherapy (e.g., severe neuropathy), and patients unwilling to receive further chemotherapy.

The evidence for gefitinib as a third-line treatment in NSCLC is more limited. However, the DSG agreed to recommend the use of the drug under specific circumstances as moderate response rates and symptom relief have been observed with gefitinib as a second- and third-line treatment. Given the limited nature of the evidence, members of the DSG suggested that treatment with gefitinib should be time limited, requiring re-evaluation one month after initiation and regularly thereafter (e.g., every two months). The continuation of treatment may be appropriate when tumour regression occurs or when stable disease with symptom improvement is evident. Toxicity associated with gefitinib administration is generally mild, although the occurrence of interstitial lung disease (ILD) is of concern.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External Review

An earlier version of this practice guideline and systematic review, dated September 16, 2004, was circulated to 135 Ontario clinicians for feedback in

September, 2004. Box 1 in the original guideline document summarizes the draft clinical recommendations and supporting evidence that was circulated to clinicians from the earlier version. Gefitinib monotherapy was recommended as a useful third-line treatment option for selected patients with advanced non-small cell lung cancer (NSCLC) who had failed prior chemotherapy involving a platinum agent and docetaxel. This recommendation was based primarily on the moderate tumour response rates and symptom relief observed with gefitinib in randomized phase II trials, the limited toxicity associated with the agent, and the fact that there was no standard third-line treatment available for these patients. Since that time, data from a key trial of gefitinib compared with placebo have become available, and the recommendations were revised.

Practitioner feedback was obtained through a mailed survey of 135 practitioners in Ontario, including 36 medical oncologists, 26 surgeons, 22 radiation oncologists, 32 respirologists, and 19 practitioners from other specialities. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on September 29, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Lung Disease Site Group (DSG) reviewed the results of the survey.

Report Approval Panel

The final Evidence-based Series report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel in October 2005. The Panel consists of two members, including an oncologist, with expertise in clinical and methodology issues. The Panel noted that the level of evidence supporting the recommendation for gefitinib monotherapy as second-line or subsequent treatment was limited, and suggested explicitly acknowledging the limitations of the evidence. The panel also suggested that the key evidence for each recommendation in the "Clinical Practice Guideline" section be distilled to the key points, given that the trial data is described in detail within the Results section of the "Systematic Review". The panel felt that, given the number of randomized trials available, data from non-randomized trials should be excluded in the future. The Lung Disease Site Group explicitly acknowledged the limitations of the evidence for gefitinib recommendation as suggested, by clarifying the evidence for this recommendation. The key evidence for each recommendation was condensed to the key points. Editorial changes were also made, in accordance with the suggestions of the Panel.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

First-line Treatment

- The addition of gefitinib or erlotinib to chemotherapy is not recommended in combination with chemotherapy or as maintenance therapy following chemoradiation as first-line treatment of advanced non-small cell lung cancer.

Treatment for Relapsed or Recurrent Disease

- Insufficient evidence exists to recommend the use of gefitinib or erlotinib over docetaxel as routine second-line treatment for relapsed or recurrent non-small cell lung cancer.
- Gefitinib monotherapy, if available, may be considered as a second-line and subsequent treatment option for selected symptomatic patients with advanced non-small cell lung cancer who are not candidates for chemotherapy and for whom erlotinib is not available.
- Erlotinib monotherapy is recommended as third-line treatment for non-small cell lung cancer patients who have failed previous chemotherapy and who maintain a good performance status. Erlotinib is also an option for second-line therapy for patients who are not candidates for second-line chemotherapy.

Treatment Duration

- The use of gefitinib or erlotinib monotherapy as a treatment for relapsed or recurrent non-small cell lung cancer should be re-evaluated one month after the initiation of therapy, and at least every two months thereafter. Treatment with gefitinib or erlotinib should be continued only when tumour regression or stable disease with symptom improvement is evident and continuing.

Treatment Dose and Schedule

- The recommended dose of gefitinib for third-line treatment of non-small cell lung cancer is 250 mg/day.
- The recommended dose of erlotinib monotherapy for the treatment of relapsed or recurrent disease is 150 mg/day.

General

- In the face of worsening respiratory symptoms associated with gefitinib administration, investigations should be undertaken to determine whether the symptoms are due to gefitinib-induced interstitial lung disease or progressive cancer.
- Insufficient evidence exists to determine which patient subgroups may benefit most from treatment with gefitinib or erlotinib.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- The results of a single randomized placebo-controlled trial revealed no statistically significant overall survival benefit for gefitinib monotherapy (250 mg/day) compared with placebo in patients who had received one or two prior chemotherapy regimens. Gefitinib was associated with a superior tumour response rate (8% versus [vs.] 1%, $p<0.0001$). Two phase II trials randomized patients to receive daily oral gefitinib at a dose of 250 mg or 500 mg for relapsed or recurrent non-small cell lung cancer. Response rate and overall survival were similar across treatment groups in both trials. Symptom response rate ranged from 35% to 43%. Although a significant survival benefit has not been demonstrated for this agent in a placebo-controlled study, the trials suggest that gefitinib may provide clinically important symptomatic benefits.
- The results from a single randomized placebo-controlled trial revealed a clinically and statistically significant survival benefit for erlotinib therapy (150 mg/day) as second or third-line systemic therapy, with a two-month absolute improvement in median survival. Although the response rate for erlotinib therapy was only 9%, significant improvements were observed in progression-free survival ($p<0.001$), overall physical quality of life (QOL) ($p=0.01$) and symptom control (cough, $p=0.04$; dyspnea, $p=0.03$; pain, $p=0.04$) in erlotinib-treated patients.
- The recommended dose of gefitinib (250 mg/day) has been shown to be equally effective as, but less toxic than, a dose of 500 mg/day. In two randomized phase II trials, each involving more than 200 patients randomized to either 250 mg or 500 mg of gefitinib daily, grade 3 or 4 toxicity was higher with the higher dose gefitinib. Interstitial lung disease-type events occurred in only one of the two trials and only with 500 mg gefitinib (2% of patients).
- A significant survival benefit was detected for a 150 mg daily dose of erlotinib monotherapy compared with placebo in one randomized placebo-controlled trial involving 731 patients previously treated with one or two chemotherapy regimens.

POTENTIAL HARMS

- Rash and diarrhea were the most frequent toxicities associated with gefitinib therapy. Other relatively common toxicities included nausea, vomiting, and ophthalmic disorders. Interstitial lung disease was relatively uncommon (0 to 2%).
- Rash and diarrhea were the most frequent toxicities associated with erlotinib therapy.
- Overall, the incidence of interstitial lung disease reported among patients given gefitinib is approximately 1%, with one third of those events being fatal.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- A number of studies have conducted exploratory subgroup analyses to identify which patients may be most responsive to treatment with an epidermal growth factor receptor (EGFR) inhibitor. Factors associated with an increased likelihood of objective tumour response following gefitinib or erlotinib monotherapy in patients with relapsed or recurrent disease include female sex, Asian origin, adenocarcinoma histology, and a history of not smoking. Although potential factors predictive for a survival benefit have been suggested in single arm trials, in the absence of a comparative treatment or placebo control group, it is difficult to determine if differences in treatment outcome by subgroup are a result of prognostic factors inherent to the subgroups or of a differential treatment interaction with the subgroup. In one randomized trial, the only factor that predicted differential *survival* benefit for erlotinib therapy was smoking history. Preliminary data from another randomized trial suggest that a survival benefit may be associated with gefitinib compared with placebo in patients who have never smoked or those of Asian origin. EGFR mutations have also been associated with responsiveness to EGFR inhibitors. In one placebo-controlled randomized trial, the survival benefit of erlotinib over placebo did not differ significantly between patients with mutations and those without EGFR mutations. At this time, there is insufficient data to indicate that EGFR inhibitors should be restricted to a specific subset of patients.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Feld R, Sridhar SS, Shepherd FA, Mackay JA, Evans WK, Lung Cancer Disease Site Group. Use of epidermal growth factor receptor inhibitors, gefitinib (Iressa®) and erlotinib (Tarceva®), in the treatment of non-small cell lung cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Jan 6. 43 p. (Evidence-based series; no. 7-9). [88 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005 Oct 17 (revised 2006 Jan 6)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Lung Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Lung Disease Site Group (DSG) disclosed potential conflict of interest information. A number of Lung Disease Site Group members, including two of the lead authors of this systematic review, have been research investigators on clinical trials of gefitinib or erlotinib, served as consultants or on advisory boards for gefitinib and erlotinib, received honoraria from the manufacturer of gefitinib (AstraZeneca) and the manufacturers and distributors of erlotinib (OSI Pharmaceuticals, Genentech, and Roche), provided expert testimony relating to gefitinib, or have ownership interests in AstraZeneca.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Use of the epidermal growth factor receptor inhibitors, gefitinib (Iressa®) and erlotinib (Tarceva®), in the treatment of non-small cell lung cancer: a clinical practice guideline. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Jan 6. Various p. (Practice guideline; no. 7-9). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on June 29, 2006. The updated information was verified by the guideline developer on July 7, 2006.

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