



Complete Summary

GUIDELINE TITLE

Chemotherapy for relapsed small cell lung cancer: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Cheng S, Evans WK, Stys-Norman D, Shepherd FA, Lung Cancer Disease Site Group. Chemotherapy for relapsed small cell lung cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Aug 2. 21 p. (Evidence-based series; no. 7-17). [13 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)

Relapsed small cell lung cancer (SCLC)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Pulmonary Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate whether chemotherapy improves survival and quality of life in patients with relapsed small cell lung cancer (SCLC)
- To evaluate which single-agent or combination chemotherapy regimen is most effective in the treatment of relapsed SCLC
- To evaluate which patients with relapsed SCLC are most likely to benefit from additional chemotherapy

TARGET POPULATION

Adult patients with relapsed small cell lung cancer (SCLC)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Retreatment with original regimen that induced initial response (generally etoposide-cisplatin; alternative regimens include cyclophosphamide, doxorubicin, and vincristine (CAV) or carboplatin and etoposide
2. Oral topotecan as an alternative

MAJOR OUTCOMES CONSIDERED

- Response rate
- Median survival (weeks and overall)
- Toxicity
- Quality of life

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

Literature Search Strategy

MEDLINE (1985 through October 2005), CANCELIT (1985 through March 2002), and the Cochrane Library (2005, Issue 4) databases were searched. Studies published prior to 1985 were excluded. Because the standard first-line treatment, since the mid-1980s, has been a platinum analogue and etoposide rather than the older regimen of cyclophosphamide, doxorubicin and vincristine (CAV), these trials would not represent the patient population receiving second-line therapy today.

"Carcinoma, small cell" (Medical subject heading [MeSH]) was combined with the MeSH terms "lung neoplasms," "neoplasm recurrence, local," "recurrence," "antineoplastic agents," "drug therapy," and "salvage therapy," and the following phrases used as text words: "small cell lung," "relapse," "recur," "refractory," "second-line," "salvage," "rechallenge," "retreat," and "reinduct." These terms were then combined with the search terms for the following publication types: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, multicentre studies, and comparative studies.

In addition, the conference proceedings of the American Society of Clinical Oncology (ASCO, 1997-2005) and the International Association for the Study of Lung Cancer (IALSC, 2005) were searched. 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, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

Study Selection Criteria

Articles published as full reports or as abstracts were selected for inclusion in this systematic review of the evidence if they were the following:

1. Randomized trials (phase II and phase III) comparing chemotherapy versus no chemotherapy or comparing different chemotherapy regimens as second-line treatment for small cell lung cancer (SCLC), and reporting data on survival or response rate
2. Evidence-based practice guidelines, systematic reviews, or meta-analyses of randomized trials on chemotherapy for patients with relapsed small cell lung cancer

The following were excluded from the systematic review of the evidence:

1. Articles published in a language other than English
2. Trials with a primary focus on first-line treatment or that included a mix of untreated and previously treated patients

NUMBER OF SOURCE DOCUMENTS

Six randomized trial 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 randomized trials were not pooled because the chemotherapy regimens used in the trials were different. The Lung Disease Site Group (DSG) will consider pooling the survival data of future fully published randomized trials 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

This evidence-based series was developed by the Lung Disease Site Group (DSG) of Cancer Care Ontario's Program in Evidence-Based Care (PEB). The series is a convenient and up-to-date source of the best available evidence on the use of chemotherapy for relapsed small cell lung cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

See the original guideline document for a discussion of the evidence used to formulate the recommendations.

Disease Site Group Consensus

Overall, the group was satisfied with the draft recommendations and document. One comment was made about the recommendations being too concise regarding specific treatment regimens for patients who responded to first-line treatment and then relapsed. As the data is limited, the DSG developed a more general statement derived from clinical expertise.

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

Report Approval Panel

Prior to the submission of this evidence-based series report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. The Panel approved the guideline as written, and only editorial changes were made in response to the suggestions of the Panel.

External Review

Feedback was obtained through a mailed survey of 57 practitioners in Ontario, including 34 medical oncologists and 23 radiation oncologists. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on June 1, 2006. 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.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- The evidence for the clinical benefit of second-line chemotherapy in the treatment of patients with relapsed small cell lung cancer (SCLC) is limited. The selection of patients for treatment with second-line therapy should be dependent on the treatment-free interval, the extent of response to first-line therapy, residual toxicity from first-line therapy, and the performance status of the patient.
- There is insufficient evidence to recommend a specific chemotherapy regimen. However, in the opinion of the Lung Cancer Disease Site Group, patients who relapse three or more months following the completion of first-line chemotherapy may benefit from retreatment with the same regimen that induced their initial response. This would generally mean retreatment with etoposide-cisplatin. Alternative regimens may include cyclophosphamide, doxorubicin, and vincristine (CAV) or carboplatin and etoposide.
- Oral topotecan is a possible alternative for patients who initially responded to chemotherapy and had a response duration of 45 days or longer.
- There is insufficient evidence to determine whether one mode of administration of topotecan is superior to any other mode of administration. Oral administration is more convenient and may be a treatment option for patients not suitable for intravenous therapy. Oral administration is

associated with a higher incidence of grade 3/4 diarrhea, whereas intravenous administration may result in a higher frequency of grade 3/4 neutropenia.

- There is currently no standard second-line chemotherapy regimen for patients who fail to respond to or who relapse shortly after first-line therapy. Clinical trials are needed to determine the optimal treatment regimen.

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

- One recent randomized phase II trial showed that chemotherapy consisting of oral topotecan and best supportive care (BSC) extended survival when compared with best supportive care alone [26 versus 14 weeks, hazard ratio (HR), 0.64; 95% confidence interval (CI), 0.45-0.90; $p=0.0104$] and improved the quality of life for patients who had relapsed, resistant small cell lung cancer (SCLC). The response rate for patients treated with oral topotecan and best supportive care was only 7%.
- One randomized phase II trial comparing cisplatin and etoposide to carboplatin, cisplatin, and etoposide found no significant differences in response rate ($p=0.20$) or survival ($p=0.11$).
- One randomized phase III trial that treated patients with cyclophosphamide, doxorubicin, and vincristine (CAV) or topotecan alone reported no significant differences in response rate ($p=0.285$) or survival ($p=0.795$).
- One phase III trial randomized patients to either bis-chloro-ethylnitrosourea [BCNU], thiotepa, vincristine, cyclophosphamide (BTOC) or etoposide and cisplatin; no significant differences in response rate ($p=0.91$) or survival ($p=0.15$) were found.
- Two randomized trials (phase II and phase III) compared oral to intravenous (IV) administration of topotecan. Response rates were 18.3% and 23.1% for oral administration and 14.8% and 21.9% for intravenous administration. Survival was not significantly different between the modes of administration (hazard ratio, 0.98; 95% confidence interval, 0.77-1.25; and risk ratio, 0.84; 95% confidence interval, 0.53-1.32).

POTENTIAL HARMS

Grade 3/4 neutropenia was the most common toxicity; 33% of patients receiving oral topotecan reported grade 4 neutropenia (see Table 2 in the original guideline document). Diarrhea (6%) and fatigue (4%) were the most commonly reported non-hematological adverse events in this group. In patients receiving best

supportive care (BSC) alone, pain (6%), dyspnea (9%), and fatigue (4%) were the most common adverse events. Mortality from all causes 30 days post-randomization was 7% for topotecan and BSC compared to 13% for BSC alone.

QUALIFYING STATEMENTS

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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

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ADAPTATION

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

DATE RELEASED

2006 Aug 2

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

The members of the Lung Disease Site Group (DSG) declared that there were no potential conflicts of interest relating to the topic of this evidence-based series.

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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:

- Chemotherapy for relapsed small cell lung cancer: a clinical practice guideline summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Aug 2. Various p. (Practice guideline; no. 7-17). 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 NGC summary was completed by ECRI on October 26, 2006. The information was verified by the guideline developer on November 24, 2006.

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Date Modified: 9/22/2008

