Evidence-based Series #7-17 VERSION 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Chemotherapy for Relapsed Small Cell Lung Cancer

Members of the Lung Cancer Disease Site Group

An assessment conducted in December 2016 deferred the review of Evidence-based Series (EBS) 7-17 Version 2, which means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document. (PEBC Assessment & Review Protocol)

This document is available on the CCO web site (http://www.cancercare.on.ca) and is comprised of the following 4 sections:

Section 1: Clinical Practice Guideline (ENDORSED)
Section 2: Systematic Review
Section 3: Guideline Development and External Review
Section 4: Document Review Summary and Tool

Release Date: May 16, 2013

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Guideline Report History

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Evidence-based Series #7-17 Version 2: Section 1

Chemotherapy for Relapsed Small Cell Lung Cancer: Guideline Recommendations

S. Cheng, W.K. Evans, D. Stys-Norman, F.A. Shepherd, and the Lung Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Lung Cancer Disease Site Group

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Summary and Review Tool for a summary of updated evidence published between 2005 and 2012, and for details on how this Clinical Practice Guideline was ENDORSED.

Report Date: December 11, 2012

Questions
1. In patients with relapsed small cell lung cancer (SCLC), does chemotherapy improve survival and quality of life?
2. Which single-agent or combination chemotherapy regimen is most effective in the treatment of relapsed SCLC?
3. Which patients with relapsed SCLC are most likely to benefit from additional chemotherapy?

Target Population
These recommendations apply to adult patients with relapsed SCLC.

Recommendations
- The evidence for the clinical benefit of second-line chemotherapy in the treatment of patients with relapsed 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.

**Key Evidence**

- One randomized phase III trial compared chemotherapy to best supportive care, three randomized trials (one phase II and two phase III) compared different second-line chemotherapy regimens, and two randomized trials (one phase II and one phase III) compared different forms of administration of second-line single-agent chemotherapy.

- One recent randomized phase II trial showed that chemotherapy consisting of oral topotecan and best supportive care (BSC) extended survival when compared with BSC 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 SCLC. The response rate for patients treated with oral topotecan and BSC 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 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], thiopeta, 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 IV administration. Survival was not significantly different between the modes of administration (HR, 0.98; 95% CI, 0.77-1.25; and risk ratio, 0.84; 95% CI, 0.53-1.32).

**Related Guidelines**
• # 7-13-1: The Role of Combination Chemotherapy in the Initial Management of Limited-Stage Small-Cell Lung Cancer;
• # 7-13-2: Prophylactic Cranial Irradiation in Small Cell Lung Cancer;
• # 7-13-3: The Role of Thoracic Radiotherapy as an Adjunct to Standard Chemotherapy in Limited-Stage Small Cell Lung Cancer.

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca
Chemotherapy for Relapsed Small Cell Lung Cancer: A Systematic Review

S. Cheng, W.K. Evans, D. Stys-Norman, F.A. Shepherd, and the Lung Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Lung Cancer Disease Site Group

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Summary and Review Tool for a summary of updated evidence published between 2005 and 2012, and for details on how this Clinical Practice Guideline was ENDORSED.

Section Date: August 2006

QUESTIONS
1. In patients with relapsed small cell lung cancer (SCLC), does chemotherapy improve survival and quality of life?
2. Which single agent or combination chemotherapy regimen is most effective in the treatment of relapsed SCLC?
3. Which patients with relapsed SCLC are most likely to benefit from additional chemotherapy?

INTRODUCTION
Lung cancer is the most common cause of cancer-related deaths in men and women. Approximately 15% to 20% of lung cancers are of the small cell type. SCLC has a very aggressive course, with approximately 60% to 70% of patients having disseminated (extensive stage) disease at presentation (1). SCLC is initially very sensitive to chemotherapy, with 60% to 90% of patients with limited-stage disease responding to first-line therapy with cyclophosphamide, doxorubicin and vincristine (CAV) or etoposide and cisplatin (EP), and 40% to 70% of patients achieving a complete response (1). Despite the high rate of response,
median survival ranges from 12 to 20 months, with only 6% to 12% of patients living beyond five years. Overall response rates (complete and partial response) are lower for patients with extensive-stage disease and range from 40% to 70%. Survival is also shorter in this population, with median survival ranging from seven to 11 months and less than 5% of patients living beyond two years (1).

Patients with SCLC who relapse or progress after first-line chemotherapy have a poor prognosis. Median survival is two to three months for patients who do not receive second-line therapy. Second-line chemotherapy produces tumour regression. However, in the majority of patients, these responses tend to be short-lived, and the median survival, even for treated patients, is rarely more than six months.

Three categories of disease have been described in the literature in relation to the response to initial chemotherapy and the duration of response: sensitive, resistant, and refractory. “Sensitive” refers to patients who have had a tumour response lasting 90 days or longer. These patients are thought to have the greatest potential for benefit from second-line chemotherapy. “Resistant” refers to patients who have recurred within 90 days of completing primary therapy. “Refractory” refers to patients with tumours that never responded to first-line therapy or those who progressed during first-line therapy. Whether or not patients with refractory or resistant SCLC benefit from second-line therapy remains a source of controversy.

There is a need to develop better treatments for patients with relapsed SCLC. The purpose of this evidence-based report is to evaluate the evidence for relapsed SCLC in order to determine the most effective therapies for this patient population.

METHODS

This systematic review was developed by Cancer Care Ontario’s (CCO) Program in Evidence-Based Care (PEBC), using the methods of the Practice Guideline Development Cycle (2). Evidence was selected by one member and reviewed by three members of the PEBC’s Lung Cancer Disease Site Group (Lung DSG) and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on the use of chemotherapy for relapsed SCLC patients. The body of evidence in this review is primarily comprised of mature randomized trial data. That evidence forms the basis of a clinical practice guideline developed by the Lung DSG. This systematic review and the companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of CCO and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

MEDLINE (1985 through October 2005), CANCERLIT (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 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 Guidelines 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 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 SCLC.

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.

Synthesizing the Evidence

The data from the randomized trials were not pooled because the chemotherapy regimens used in the trials were different. The Lung 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.

RESULTS

Literature Search Results

Six randomized trials met the pre-defined eligibility criteria for this systematic review (3-8). Of those, four were fully published reports (4-6,8), and two were in abstract form (3,7). One randomized phase III trial compared chemotherapy to best supportive care (3), three randomized trials (one phase II (4) and two phase III (5,6)) compared different second-line chemotherapy regimens, and two randomized trials (one phase II (8) and one phase III (7)) compared different forms of administration of second-line single-agent chemotherapy. Treatment regimens, study descriptions, and outcomes are shown in Table 1. No relevant systematic reviews or evidence-based clinical practice guidelines were identified.

One retrieved meta-analysis pooled patient data from five trials of single-agent topotecan (9). This analysis was excluded as it was not conducted systematically and included non-randomized trials. A recent review on treatment of recurrent SCLC was also retrieved (10). This review was not systematic and included single arm non-comparative trials and, therefore, also did not meet the inclusion criteria.

<table>
<thead>
<tr>
<th>Table 1. Randomized trials for the treatment of relapsed SCLC.</th>
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<td>Reference</td>
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<tr>
<td><strong>Chemotherapy versus best supportive care</strong></td>
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### Comparing different second-line chemotherapy regimens

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility Criteria</th>
<th>Response Rate (CNS Metastases)</th>
<th>Survival (CNS Metastases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCLC that relapsed &gt;45 days after achieving response to first-line CT, ineligible for further IV CT, ECOG PS 0-2</td>
<td>PO Topotecan 2.3 mg/m²/d, days 1-5, q21d + BSC (PO Topo)</td>
<td>7% [0/5/31]</td>
<td>25.9 HR 0.64 (95% CI, 0.45-0.90) p=0.0104</td>
</tr>
<tr>
<td>Phases II and III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCLC that failed or relapsed after first line CT, Karnofsky PS ≥ 60, no previous platinum or etoposide</td>
<td>Cisplatin 20 mg/m² + Etoposide 100 mg/m² d 1-3 q3w (EP)</td>
<td>29% [0/9/4]</td>
<td>18.7 p=0.11</td>
</tr>
<tr>
<td>Phases II and III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCLC with progression ≥ 60 days after first line CT, ECOG PS 0-2, no prior topotecan, only one previous CT regimen, symptomatic CNS metastases not allowed if corticosteroids required</td>
<td>Cyclophosphamide 1000 mg/m² + Doxorubicin 45 mg/m² + Vincristine 2 mg d1, q3w (CAV)</td>
<td>18.3% [1/18/12]</td>
<td>24.7 p=0.795</td>
</tr>
<tr>
<td>Phases III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCLC that failed or relapsed after first-line CT, recovered from prior therapy, Karnofsky PS ≤ 3, no previous line EP or BTOC</td>
<td>PO Topotecan 1.5 mg/m²/d for 5d, q21d (PO Topo)</td>
<td>24.3% [0/26/21]</td>
<td>25.0</td>
</tr>
<tr>
<td>Phases III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCLC recurring ≥ 90 days from first-line CT, only one prior CT regimen, ECOG PS ≤ 2, documented CR or PR to first line CT</td>
<td>Cisplatin 50(P)-75(G) mg/m² d2 + Etoposide 100(P)-125(G) mg/m² d1,3,4 (EP)</td>
<td>12.1% [1/6/NR]</td>
<td>16 p=0.15</td>
</tr>
<tr>
<td>Phases III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCLC recurring ≥ 90 days after first-line CT, only one prior CT regimen, WHO PS ≤ 2, documented PR or CR to first line CT</td>
<td>Bis-Chloro-EthylNitrosourea 75(P) - 100(G) mg/m² + Thiotepa 20mg/m² + Vincristine 2mg + Cyclophosphamide 375(P) - 500(G) mg/m² d1,21,42 (BTOC)</td>
<td>13.3% [0/6/NR]</td>
<td>p=0.91</td>
</tr>
</tbody>
</table>

### Comparing different administration of second-line single agent chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility Criteria</th>
<th>Response Rate (CNS Metastases)</th>
<th>Survival (CNS Metastases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCLC recurring ≥ 90 days from first-line CT, only one prior CT regimen, ECOG PS ≤ 2, documented CR or PR to first line CT</td>
<td>PO Topotecan 2.3 mg/m²/d for 5d, q21d (PO Topo)</td>
<td>18.3% [2/26/27]</td>
<td>33 HR 0.98 (95% CI, 0.77-1.25)</td>
</tr>
<tr>
<td>Phases III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCLC recurring ≥ 90 days after first-line CT, only one prior CT regimen, WHO PS ≤ 2, documented PR or CR to first line CT</td>
<td>IV Topotecan 1.5mg/m²/d for 5d, q21d (IV Topo)</td>
<td>21.9% [0/33/35]</td>
<td>35</td>
</tr>
<tr>
<td>Phases III</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

### Abbreviations
- BSC: best supportive care
- CR: complete response
- CT: chemotherapy
- d: day(s)
- ECOG: Eastern Cooperative Oncology Group
- HR: hazard ratio
- IV: intravenous
- LD: limited disease
- mets: metastasis
- N: number of patients
- NA: not available
- NR: not reported
- OR: oral
- PR: partial response
- PS: performance status
- q: every
- RR: risk ratio
- SCLC: small cell lung cancer
- SD: stable disease
- WHO: world health organization

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**Outcomes**

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Section 2: Systematic Review
Chemotherapy versus Best Supportive Care

One open-label phase III trial randomized 141 relapsed SCLC patients ineligible for further intravenous (IV) chemotherapy to oral topotecan combined with best supportive care (BSC) or BSC alone (3). This trial, published in abstract form only, provided limited data on which to assess the trial quality. Eligible patients had to have relapsed at least 45 days after achieving a response to first-line chemotherapy, have a performance status (PS) Eastern Cooperative Oncology Group (ECOG) ≤2, and be ineligible for further IV chemotherapy. Patients were stratified by PS, gender, presence of liver metastases at baseline, and time to progression from the end of chemotherapy (≤ 60 versus [vs] > 60 days). The primary outcome was overall survival. The final analysis yielded 80% statistical power for the primary outcome. The median number of courses of oral topotecan administered was four.

Tumour response and survival

The overall response rate for oral topotecan and BSC was 7% (95% CI 2.3%-15.7%), although no patients achieved a complete response. The stable disease rate was 44% (31 of 77 patients) for patients receiving topotecan. A comparison of survival outcomes revealed a statistically significant benefit for oral topotecan and BSC compared with BSC alone; hazard ratio (HR) 0.64, 95% CI 0.45-0.90, p=0.0104. Six-month survival rates were 48.8% for oral topotecan and BSC compared to 25.7% for BSC alone. Subgroup analyses demonstrated a significant survival benefit for patients with a time to progression of ≤60 days (23 weeks vs 13 weeks, p=0.0357) but not for patients with a time to progression of ≥60 days (28 weeks vs 14 weeks, p=0.0975).

Toxicity

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

Quality of Life

The standardized EuroQoL Group EQ-5D questionnaire was used to measure quality of life at baseline and at three-month intervals (3). The rate-of-change analysis demonstrated a statistically significant faster rate of decline in the BSC alone arm as compared with the topotecan and BSC arm.
Table 2. Grade 3/4 toxicities for randomized trials.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Neutropenia</th>
<th>Leukopenia</th>
<th>Thrombocytopenia</th>
<th>Anemia</th>
<th>Nausea/Vomiting</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sculier, 2002 (4)</td>
<td>EP</td>
<td>58%</td>
<td>16%</td>
<td>NR</td>
<td>6%</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EPCb</td>
<td>53%</td>
<td>35%</td>
<td>NR</td>
<td>0%</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>von Pawel, 1999 (5)</td>
<td>CAV</td>
<td>87%</td>
<td>15%</td>
<td>20%</td>
<td>6%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Topo</td>
<td>88%</td>
<td>58%</td>
<td>42%</td>
<td>4%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>O'Bryan, 1990 (6)</td>
<td>EP</td>
<td>14%</td>
<td>9%</td>
<td>NR</td>
<td>0%</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BTOC</td>
<td>16%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>von Pawel, 2001 (8)</td>
<td>PO Topo</td>
<td>47%</td>
<td>28.7%</td>
<td>22.6%</td>
<td>3.9%/3.3%</td>
<td>7.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV Topo</td>
<td>64%</td>
<td>18%</td>
<td>30.7%</td>
<td>2.6%/2%</td>
<td>1.3%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Comparing different administration of second-line single agent chemotherapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Neutropenia</th>
<th>Leukopenia</th>
<th>Thrombocytopenia</th>
<th>Anemia</th>
<th>Nausea/Vomiting</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eckardt, 2003 (7)</td>
<td>PO Topo</td>
<td>56.9%</td>
<td>45.1%</td>
<td>53%</td>
<td>31.4%</td>
<td>0%/11.5%</td>
<td>7.7%</td>
</tr>
<tr>
<td></td>
<td>IV Topo</td>
<td>94.2%</td>
<td>73.6%</td>
<td>49%</td>
<td>30.2%</td>
<td>0%/3.7%</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: BSC - best supportive care, BTOC - bis-chloro-ethylnitrosourea, thiopeta, vincristine, cyclophosphamide, CAV - cyclophosphamide, doxorubicin, vincristine, EP - etoposide, cisplatin; EPCb - etoposide, cisplatin, carboplatin, IV - intravenous, NR - not reported, PO - oral, Topo - topotecan.

- Calculated based on number of patients with laboratory data available.
- Statistical analyses for courses, not by patient.
- Grade 4 toxicity

Second-Line Chemotherapy Regimens

Three randomized trials, including two phase III and one phase II, investigated different chemotherapy regimens for patients with relapsed SCLC (4-6). Sculier et al (4) randomized 72 patients to receive EP with or without carboplatin as second-line therapy. von Pawel et al (5) randomized 211 patients to IV topotecan or CAV. O'Bryan et al (6) randomized 103 patients to bis-chloro-ethylnitrosourea, thiopeta, vincristine, and cyclophosphamide (BTOC) or EP. Two trials described the randomization process (4,5), and one reported the
method of sample size determination (4). Patients were stratified by centre, PS, and disease-free interval in one trial (4), and by extent of disease and PS in another (5). Response was the primary outcome in two trials (4,5), and comparisons of both response and survival were the objectives in the third trial (6). None of the trials reported on the blinding of treatment assignment for patients or physicians; however, independent radiologists blinded to treatment assignment reviewed the radiographs of all responders in the trial by von Pawel et al (5). One trial reported pharmaceutical support (5). O’Bryan et al (6) randomized 103 patients, but also reported on an additional 26 non-randomized eligible patients who were treated with EP. Sculier et al (4) randomized 72 patients, but seven were later considered ineligible, and six were not assessable for response. There was also an imbalance between the treatment groups in the number of patients excluded. These factors suggest that the trial results should be interpreted with caution. In addition, Sculier et al excluded patients if their previous chemotherapy contained a platinum or etoposide, and therefore, this trial is less relevant for current practice.

**Tumour response and survival**

None of the trials examining different second-line chemotherapy regimens detected a statistically significant difference in tumour response or survival between treatment arms (4-6). The trial by Sculier et al (4) was not powered to assess survival differences, and median survival was 18.7 weeks for EP and 33.1 weeks for EP and carboplatin (p=0.11). Sculier et al (4) reported response rates of 47% in the carboplatin and EP arm versus 29% in the EP-alone arm. Survival was not significantly different (7.4 months vs 7.7 months) when analysed by the treatment-free interval between first-line and second-line treatment (<3 months vs >3 months), regardless of the treatment arm. However, patients who responded to first-line treatment and had a treatment-free interval of greater than three months had significantly higher response rates than patients with a treatment free interval of less than three months (4). von Pawel et al (5) reported similar median survival rates for patients treated with topotecan (25.0 weeks) or CAV (24.7 weeks) (p=0.795). The response rate for patients receiving topotecan was 24.3%, compared to 18.3% for CAV. Cox regression analysis, which adjusts for the effect of multiple predictor variables on survival, was statistically significant for baseline PS and extent of disease (p<0.001). O’Bryan et al (6) investigated different dose schedules for patients who were assessed as good or poor risk. The median survival was 13 weeks for patients receiving BTOC (10 weeks for good risk and 14 weeks for poor risk) and 16 weeks for patients treated with EP (35 weeks for good risk and 12 for poor risk patients). A subgroup analysis detected a statistically significant survival difference between the two arms in the good risk patients (p=0.01) in favour of treatment with EP. The response rate was 13% (6 partial responses [PR]) in the BTOC arm and 12% (1 complete response [CR], 6 PR) in the EP arm. Response rates were not reported for the 26 non-randomized patients.

The observed differences between the two phase III trials in response rates and survival may be due to differences in the patient populations. Most patients in the trial by von Pawel et al had received platinum-based first line chemotherapy (77-79%) and had all responded to first-line chemotherapy, with most patients relapsing more than 60 days after initial treatment. The majority of patients also exhibited a good PS (ECOG 0-1, 79%) (5). However, in the trial by O’Bryan et al, most patients (72%) received CAV or single-agent etoposide as first-line treatment, with a median treatment-free interval of only six weeks and a generally poor PS (Karnofsky 2-3, 56%) (6).

**Toxicity (Table 2)**

Sculier et al (4), reported comparable toxicity between both treatment arms, except for grade 3 or 4 thrombocytopenia, which was more common with the carboplatin regimen.
(35% vs 16%, p=0.09). Infections were reported in 3% of patients in both arms, and there was one treatment-related death in the EP arm.

von Pawel et al (5) reported a similar incidence of grade 4 neutropenia in both treatment arms (topotecan, 70.2%; CAV, 71.7%). However, significantly more grade 4 thrombocytopenia (57.6% vs 14.9%, p<0.001) and grade 3/4 anemia (42.3% vs 19.8%, p<0.001) occurred in the topotecan arm. Transfusions were more frequent among patients treated with topotecan and included platelet transfusions (19.6% vs 1.9% of patients) and red blood cell transfusions (52.3% vs 26.9% of patients, p<0.001). There were seven treatment-related deaths associated with myelosuppression and infection, four in the topotecan-treatment group and three in the CAV-treatment group. Three additional deaths were possibly treatment related, two associated with topotecan (acute respiratory insufficiency and intracerebral hemorrhage) and one associated with CAV (disease progression coincident with renal failure and pancytopenia). Twenty patients withdrew from study treatment due to treatment-related toxicity, ten in the topotecan group and ten in the CAV group (5).

O’Bryan et al (6) reported grade 4 neutropenia in 8.9% of patients treated with BTOC and 13.6% of patients treated with EP. Thrombocytopenia was reported in 15.5% and 8.6% of patients for the BTOC and EP treatment groups, respectively. Parethesias were reported for 12 patients (15%) treated with EP and four patients (9%) receiving BTOC. There were three treatment-related deaths, two from infection and myelosuppression (one in each treatment group) and one, in the EP group, from gastrointestinal bleeding associated with thrombocytopenia. The 26 non-randomized patients from the EP group were included in the toxicity results.

Quality of Life

Quality of life was not assessed in any of the trials that compared different second-line chemotherapy regimens. von Pawel et al did assess disease-related symptoms on a patient-reported four-point scale. Symptom improvement was significantly greater for patients receiving topotecan, with improvements reported in dyspnea (p=0.002), hoarseness (p=0.043), fatigue (p=0.032), anorexia (p=0.042), and interference with daily activities (p=0.023) (5).

Administration of Second-Line Single-Agent Chemotherapy

Two randomized trials, one phase III (7) and one phase II (8), evaluated the administration of oral versus IV topotecan in patients who had relapsed after first-line treatment (7,8). The phase III trial was published in abstract form only and provided limited data on which to assess the trial quality. The phase II trial focused on the efficacy of administration (8), while the phase III trial (7) reported initial findings on the effectiveness of administering oral topotecan versus IV topotecan. The number of patients randomized to IV or oral topotecan was 106 for the phase II trial and 304 for the phase III trial. Neither trial described the randomization process in detail. The phase III trial determined sample size based on the feasibility of study completion (7). The phase III trial stratified patients by response duration to prior chemotherapy, gender, and presence or absence of liver metastases (7). The phase II trial stratified patients by extent of disease, duration of response to prior chemotherapy, and presence or absence of liver metastases (8). Response was the primary outcome in the phase III trial (7), and response, response duration, and time to progression were primary objectives in the phase II trial (8). None of the trials reported on the blinding of treatment assignment for patients or physicians; however, both trials had blinded independent radiologists review the radiographs. Both trials also reported pharmaceutical support (5). The median number of courses of topotecan administered was four (7,8).
Tumour response and survival

Eckardt et al (7) reported overall response rates of 18.3% (two CR and 26 PR) for patients treated with oral topotecan and 21.9% (33 PR) for patients receiving IV topotecan. One-year survival rates were 33% and 29%, respectively, and the median survival was 33 and 35 weeks for the oral group versus the IV group (HR, 0.98; 95% CI, 0.77-1.25). von Pawel et al (8) found overall response rates of 23.1% (one CR and 11 PR) for oral administration and 14.8% (two CR and six PR) for IV administration; with median overall survival rates of 32.3 and 25.1 weeks (risk ratio, 0.84; 95% CI, 0.53-1.32), respectively. Factors statistically associated with longer survival in a Cox regression analysis were baseline liver metastases (p=0.001) and PS (p=0.025).

Toxicity (Table 2)

Eckardt et al (7) reported treatment-related grade 4 neutropenia in 47% of the patients treated orally and 64.2% patients treated intravenously. Febrile neutropenia was reported in 4.6% and 7.3% for the oral group versus the IV group, respectively; the incidence of diarrhea was statistically significantly higher in the oral group (7.9% vs 1.3%, p<0.05). Infection was reported in both groups (9.8% vs 7.9%, respectively), as was sepsis (2.6% vs 3.3%) and dehydration (3.9% vs 1.3%). There were ten treatment-related deaths, six (4%) in the oral group and four (3%) in the IV group.

von Pawel et al (8) noted toxicity in both arms of the study. Grade 3 or 4 neutropenia was present in 56.9% of the patients treated orally versus 94.2% of the patients treated intravenously. Grade 3/4 dyspnea presented in 9.6% of the patients on oral therapy and 9.3% on IV therapy. Incidences of grade 3/4 fever, pneumonia, and diarrhea were greater in the oral topotecan arm (5.8%, 7.7%, and 7.7%) when compared with the IV arm (1.9%, 0%, and 0%). Grade 5 dyspnea and pneumonia were reported in two patients treated with IV topotecan; grade 5 fever occurred in one patient in the oral arm. Grade 5 pulmonary embolism occurred in 3.8% of the oral and 1.9% of the IV patients. Red blood cell transfusions were given to 42.3% and 38.9% of patients, and platelet transfusions were given to 13.5% and 14.8% of patients receiving oral and IV topotecan, respectively. There were two treatment-related deaths in the oral-topotecan arm.

Quality of Life

Eckardt et al did not find a statistically significant difference in quality of life as assessed by the Functional Assessment of Cancer Therapy-Lung (FACT-L), Trial Outcome Index (TOI), individual well-being, or individual symptom scores (7). von Pawel et al also measured the quality of life but used a non-validated instrument that was based on the Lung Cancer Symptom Score (8). Self-assessed symptoms were measured at baseline and immediately before the next therapy. For patients initially reporting symptoms, treatment with either oral or IV topotecan improved the following from baseline: chest pain (42.1 and 31.8% of patients, respectively), hemoptysis (33.3 and 40%), insomnia (32 and 26.6%), hoarseness (35.7 and 37.5%), and interference with daily activity (25.8 and 22.2%).

DISCUSSION

Evidence for the clinical benefit of second-line chemotherapy in the treatment of patients with relapsed SCLC is limited. However, the recently reported randomized phase III trial of topotecan and BSC versus BSC alone (3) is the first to demonstrate an improvement in overall survival and quality of life in patients with relapsed, resistant SCLC. The preliminary results from this trial showed a statistically significant difference in overall survival (p=0.0104), favouring treatment with topotecan and BSC. Patients treated with oral
topotecan and BSC had a median survival of 26 weeks compared with 14 weeks for those who received BSC alone. Furthermore, the quality of life of patients who received topotecan and BSC was found to be superior to BSC alone; and symptom control was also improved.

Three randomized trials (two phase III and one phase II) have compared different chemotherapy regimens. No statistically significant difference was found in median survival rates for the two phase III trials [24.7 and 25.0 weeks (5), respectively, and 13 and 16 weeks (6)]. The differences in survival between these two studies can likely be accounted for by differences in the patient populations between the trials. Most patients in the O’Bryan study had received either CAV or etoposide alone as first-line therapy, the median time from last treatment was only six weeks, and the patients generally had a poor PS (6). However, most patients in the trial by von Pawel et al received platinum-based first-line chemotherapy, had responded to first-line chemotherapy (with most relapsing more than 60 days after initial treatment), and exhibited a good PS (5). Thus, the O’Bryan et al trial consisted of a group of patients with poorer prognostic factors than von Pawel et al, which might explain the lesser degree of benefit from therapy found in this trial. Furthermore, the O’Bryan et al trial is less relevant to recommendations for second-line therapy in SCLC in North America and Europe today, as first-line SCLC patients are currently treated with EP. Only the study by von Pawel et al (5) reported a benefit in symptom management with topotecan in comparison to CAV. However, the scoring system for this measure was not validated. Nonetheless, on the basis of the demonstrated improvement in cancer-related symptoms found in the von Pawel et al trial, the US Food and Drug Administration approved single-agent topotecan as a therapy for relapsed SCLC.

There is no clinical evidence to suggest that combination chemotherapy regimens are superior to single-agent regimens in the treatment of relapsed SCLC. Only one phase III study compared combination therapy (CAV) to a single agent (topotecan), and response rates and median survival were equivalent between the trial arms (5). However, there was more hematologic toxicity and a greater need for transfusion in the topotecan arm. Eckardt et al (7) and von Pawel et al (8) both found similar response rates and median survival rates for both the oral and IV administration of topotecan. The response rates with oral administration were 18.3% and 23.1%, compared to 21.9% and 14.8% among IV-treated patients. Both studies noted that diarrhea was more prevalent among patients treated with oral topotecan when compared with those receiving IV administration. However, neutropenia was higher in the IV arm. Both trials concluded that oral topotecan is a viable option for patients not suitable for IV therapy.

There is limited evidence to determine which patients are most likely to benefit from second-line chemotherapy. A poor PS and relapse within six weeks of completing first-line chemotherapy (resistant disease) are generally recognized as poor prognostic factors and predict lower response rates and shorter survival in SCLC. A pooled analysis, which did not meet the criteria for inclusion in this review, was conducted on five trials of single-agent topotecan administered at time of relapse. This analysis compared outcomes for patients with a PS ECOG 0-1 to those with an ECOG >2 (9). The overall response rate for patients with PS 0/1 was 14% (11 CR and 42 PR) compared to 17% for PS 2 patients (three CR and 14 PR). Response rates were lower for patients with chemoresistant or refractory disease, compared to chemosensitive patients, regardless of PS. Median survival times were 36.3 weeks, 25.4 weeks and 16 weeks for PS 0, PS 1, and PS 2 respectively. Survival was significantly different between PS 0/1 patients and PS 2 patients (p<0.001) (9). Thus, adequate assessment of PS is important when evaluating treatment options for relapsed SCLC patients, as patients with poor PS may not derive meaningful benefit from second-line treatment.
ONGOING TRIALS

The National Cancer Institute (NCI) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and the ASCO conference proceedings (1997-2005) were searched for reports of new or ongoing trials. No ongoing randomized trials evaluating chemotherapy for relapsed SCLC were identified.

CONCLUSIONS

Evidence for the clinical benefit of second-line chemotherapy in the treatment of patients with relapsed SCLC is limited. The randomized phase III trial of topotecan and BSC versus BSC alone (3), reported in abstract form only, has demonstrated a significant improvement in overall survival and quality of life in patients with relapsed SCLC after an initial response to chemotherapy of at least 45 days duration. This data suggest that oral topotecan in combination with BSC is a treatment option for patients who have previously responded to first-line therapy, if the response duration is reasonably long. There is insufficient evidence to recommend a specific chemotherapy regimen. 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 refer to retreatment with etoposide-cisplatin. Alternative regimens may include 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 which mode of administration of oral topotecan is most effective. Oral administration is more convenient but is associated with a higher incidence of grade 3/4 diarrhea, whereas IV administration may result in a higher frequency of grade 3/4 neutropenia.

There is currently no standard protocol for second-line therapy for patients who fail to respond to or who relapse very shortly after first-line therapy. Clinical trials are needed to determine the best treatment for patients in this situation.

CONFLICT OF INTEREST

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

JOURNAL REFERENCES


ACKNOWLEDGEMENTS

The Lung DSG would like to thank Drs. Susanna Cheng, William K. Evans, and Frances A. Shepherd, Mrs. Denise Stys-Norman, and Ms. Jessica A. Vanderveen for taking the lead in drafting this systematic review.
REFERENCES

Evidence-Based Series #7-17 Version 2: Section 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Chemotherapy for Relapsed Small Cell Lung Cancer: Guideline Development and External Review—Methods and Results

S. Cheng, W.K. Evans, D. Stys-Norman, F.A. Shepherd, and the Lung Cancer Disease Site Group

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Summary and Review Tool for a summary of updated evidence published between 2005 and 2012, and for details on how this Clinical Practice Guideline was ENDORSED.

Report Date: December 11, 2012

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs) mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the periodic review
and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-Based Series: A New Look to the PEBC Practice Guidelines

Each evidence-based series is comprised of three sections:

- **Section 1: Clinical Practice Guideline.** This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.

- **Section 2: Systematic Review.** This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.

- **Section 3: Guideline Development and External Review - Methods and Results.** This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

**Development and Internal Review**

This evidence-based series was developed by the Lung DSG of Cancer Care Ontario’s PEBC. 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.

**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.

**Report Approval Panel**

Prior to the submission of this evidence-based series report for external review, the report was reviewed and approved by the 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 by Ontario Clinicians**

Following the review and discussion of Sections 1 and 2 of this evidence-based series and review and approval of the report by the PEBC Report Approval Panel, the Lung DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

**BOX 1:**

<table>
<thead>
<tr>
<th>Draft Recommendations (approved for external review June 1, 2006)</th>
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<tr>
<td><strong>Target Population</strong></td>
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<tr>
<td>These recommendations apply to adult patients with relapsed SCLC.</td>
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<tr>
<td><strong>Recommendation</strong></td>
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</table>
The evidence for the clinical benefit of second-line chemotherapy in the treatment of patients with relapsed 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 which mode of administration of topotecan is most effective. 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.

Methods
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 DSG reviewed the results of the survey.

Results
Twenty-nine responses were received out of the 57 surveys sent (51% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 16 indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.

Table 1. Responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
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<tr>
<td></td>
<td>Strongly agree or agree</td>
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<tr>
<td>The rationale for developing a guideline, as stated in the “Introduction” section of the report, is clear.</td>
<td>15 (94%)</td>
</tr>
<tr>
<td>There is a need for a guideline on this topic.</td>
<td>12 (75%)</td>
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<tr>
<td>The literature search is relevant and complete.</td>
<td>13 (81%)</td>
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<tr>
<td>The results of the trials described in the report are</td>
<td>14 (88%)</td>
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</table>
Summary of Written Comments

Six respondents (40%) provided written comments, most of which indicated their support for the summary of evidence and final recommendations. There were three issues raised that required a response by the DSG.
1. Two respondents indicated that the evidence in this topic area is very limited and that more data is needed on quality of life.
2. One practitioner stated that they would offer single agent oral etoposide to patients, despite lack of clinical trial evidence, based on remissions achieved with this agent in clinical practice.
3. One practitioner suggested that topotecan should be the drug of choice for second-line therapy in suitable patients as CAV is not effective for patients who have relapsed from platinitol-etoposide.

Modifications/Actions

The DSG responses to the above comments are summarized below.
1. The DSG acknowledges that the evidence is very limited evidence for second-line chemotherapy in SCLC patients and that future trials should include quality of life.
2. The DSG recognizes that physicians may have individual experiences showing benefit with single-agent oral etoposide. However, this is an evidence-based guideline and the DSG decided not to recommend single-agent oral etoposide as insufficient evidence exists to recommend its use in this population.
3. The DSG does not agree with the statement regarding the lack of sensitivity of SCLC patients to combination chemotherapy with CAV. There is currently no randomized evidence that CAV should not be used in the second line setting. The von Pawel trial (3) randomized patients who failed or relapsed after first-line chemotherapy to CAV or topotecan and reported no significant differences in survival or response rates between the treatment arms. The DSG did not revise the recommendation as the available evidence supports the use CAV as an option for relapsed SCLC patients.

Policy Review

This practice guideline report will be submitted to the Oncology Subcommittee of the Drug Quality and Therapeutics Committee, in order to obtain approval for the funding of topotecan for relapsed SCLC patients.
REFERENCES


Evidence-based Series #17- 7 Version 2: Section 4

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Chemotherapy for Relapsed Small Cell Lung Cancer: Guideline Review Summary

S. Cheng, R. Mackenzie
and the Lung Cancer Disease Site Group

Review Date: December 11, 2012

The 2006 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

Evidence-based Series History

The original version of this guidance document was released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario in 2006. In September 2011, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (SC) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Lung Cancer Disease Site Group (DSG) endorsed the recommendations found in Section 1 (Clinical Practice Guideline) on December 11, 2012.
DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered
1. In patients with relapsed small cell lung cancer (SCLC), does chemotherapy improve survival and quality of life?
2. Which single agent or combination chemotherapy regimen is most effective in the treatment of relapsed SCLC?
3. Which patients with relapsed SCLC are most likely to benefit from additional chemotherapy?

Literature Search and New Evidence
The new search (October 2005 to October 2012) yielded 12 relevant new publications in the following categories: Two Randomized Control Trials, two systematic reviews (one meta-analysis, 7 existing guidelines and one abstract). Brief results of these publications are shown in the Document Assessment and Review Tool at the end of this report.

Impact on Guidelines and Its Recommendations
The new data supports existing recommendations. Hence, the Lung Cancer DSG ENDORSED the 2006 recommendations on chemotherapy for relapsed small cell lung cancer.

Document Summary and Review Tool

| Number and title of document under review | 7-17 Chemotherapy for Relapsed Small Cell Lung Cancer |
| Current Report Date | October 8, 2012 |
| Clinical Expert | Dr. Susanna Cheng |
| Research Coordinator | Robert Mackenzie |
| Date Assessed | Nov 9, 2012 |
| Approval Date and Review Outcome (once completed) | December 11, 2012 (ENDORSE) |

Original Question(s):
1. In patients with relapsed small cell lung cancer (SCLC), does chemotherapy improve survival and quality of life?
2. Which single-agent or combination chemotherapy regimen is most effective in the treatment of relapsed SCLC?
3. Which patients with relapsed SCLC are most likely to benefit from additional chemotherapy?

Target Population:
- Adult patients with relapsed SCLC.

Study Selection Criteria:
Inclusion 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:
- Randomized trials (phase II and phase III) comparing chemotherapy versus no chemotherapy or comparing different chemotherapy regimens as second-line treatment for SCLC, and reporting data on survival or response rate.
- Evidence-based practice guidelines, systematic reviews, or meta-analyses of randomized trials on chemotherapy for patients with relapsed SCLC.

Exclusion Criteria
- Articles published in a language other than English.
- Trials with a primary focus on first-line treatment or that included a mix of untreated and previously treated patients.
## Brief Summary/Discussion of New Evidence:

### COMPARATIVE RANDOMIZED CONTROL TRIALS

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Name of RCT (med F/U)</th>
<th>Population (n)</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>amrubicin (AMR) versus topotecan (Topo)</td>
<td>Results of a randomized phase II trial of amrubicin (AMR) versus topotecan (Topo) in patients with extensive-disease small cell lung cancer (ED-SCLC) sensitive to first-line platinum-based chemotherapy</td>
<td>n=76</td>
<td>Overall response rate (ORR), progression free survival, Overall survival</td>
<td>AMR significantly improved overall response rate (P&lt;0.012), AMR showed increased pfs/os 4.3mo/9.3mo vs 3.5mo/8.9mo.</td>
<td>Jotte R., et al. (2009)</td>
</tr>
<tr>
<td>Best Supportive Care versus oral topotecan</td>
<td>Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer</td>
<td>n=141</td>
<td>Survival, Quality of Life</td>
<td></td>
<td>O'Brien ME., et al.</td>
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### ABSTRACTS

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Name of RCT (med F/U)</th>
<th>Population (n)</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topotecan (T) (oral and IV) vs Topotecan (T) (oral and IV) and AVE0005 (afibercept) (A)</td>
<td>SWOG 0802: A randomized phase II trial of weekly topotecan with and without AVE0005 (afibercept) in patients with platinum-treated extensive-stage small cell lung cancer (E-SCLC)</td>
<td>n=96</td>
<td>Progression free survival</td>
<td>3-month PFS was 26% for A+T versus 9% for T (P=0.01)</td>
<td>Allen J., et al.</td>
</tr>
</tbody>
</table>

  Overall survival was similar in each arm (4.6 mos (A+T) versus 3.9 mos (T) (P=0.25)).
  There was 1 partial response with A+T.
  Disease control rate (DCR) was 28% with A+T and 12% with T.
  Toxicity was mainly moderate.
There was one treatment-related death with T (renal failure).

**SYSTEMATIC REVIEWS**

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Name of RCT (med F/U)</th>
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</thead>
<tbody>
<tr>
<td>Effectiveness of second-line chemotherapy compared with BSC or placebo in prolonging survival in patients with extensive SCLC at relapse or progression</td>
<td>Chemotherapy versus best supportive care for extensive small cell lung cancer</td>
<td>n=531</td>
<td>Median, 6 mo., 1 yr., 2yr. Survival, Tumor response, Toxicity, Quality of Life</td>
<td>In O'Brien 2006, treatment with topotecan at relapse gave a median survival time of 84 days longer than in the BSC group (logrank P = 0.01)</td>
</tr>
<tr>
<td>Oral topotecan vs intravenous topotecan or best supportive care and intravenous topotecan vs cyclophosphamide, adriamycin and vincristine(cav)</td>
<td>Systematic Review of topotecan (Hycamtin) in relapsed small cell lung cancer</td>
<td>n=762</td>
<td>Survival, response rates, toxicity, quality of life.</td>
<td>Oral topotecan plus BSC resulted in improved survival over BSC alone (hazard ratio = 0.61; 95% CI, 0.43 to 0.87)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Intravenous topotecan was at least as effective as cav and resulted in improved quality of life.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For oral &amp; IV topotecan groups: Survival (hazard ratio = 0.98; 95% CI, 0.77 to 1.25) and response (pooled risk ratio = 1.04; 95% CI, 0.58 to 1.85). Symptom control was also very similar between the trials and between the oral and IV groups.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Toxicity data showed a significant difference in favour of oral topotecan vs IV for neutropenia (pooled risk ratio = 0.65; 95% CI, 0.47 to 0.89)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Indirect evidence showed that oral topotecan was at least as good as or better than CAV on</td>
</tr>
</tbody>
</table>
### ON-GOING CLINICAL TRIALS (Retrieved from clinicaltrial.gov database)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Official title</th>
<th>Status</th>
<th>Protocol ID &amp; URL</th>
<th>Last Updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picoplatin and BSC Versus BSC Alone</td>
<td>A Randomized, Controlled Phase III Trial of Picoplatin and BSC Versus BSC Alone in Patients With Small Cell Lung Cancer (SCLC), Refractory or Progressive Within Six Months of Completing First-Line, Platinum-Containing Chemotherapy.</td>
<td>unknown</td>
<td>NCT00465491</td>
<td>April 13, 2009</td>
</tr>
<tr>
<td>Oral Topotecan Versus Intravenous Topotecan</td>
<td>An Open Label, Multicenter, Randomized, Phase III Comparator Study of Oral Topotecan Versus Intravenous Topotecan for Second Line Therapy in Patients With Small Cell Lung Cancer Who Have Relapsed Greater Than or Equal to 90 Days After Completion of First Line Therapy</td>
<td>unknown</td>
<td>NCT00003917</td>
<td>February 10, 2011</td>
</tr>
<tr>
<td>Drug: linsitinib</td>
<td>Randomized Phase II Study of Single Agent OSI-906, an Oral, Small Molecule, Tyrosine Kinase Inhibitor (TKI) of the Insulin Growth Factor-1 Receptor (IGF-1R) Versus Topotecan for the Treatment of Patients With Relapsed Small Cell Lung Cancer (SCLC)</td>
<td>recruiting</td>
<td>NCT01533181</td>
<td>July 12, 2012</td>
</tr>
<tr>
<td>Drug: Amrubicin</td>
<td>A Randomized Phase 2 Trial Comparing Amrubicin Versus Topotecan as Second-Line Treatment in Patients With Extensive Small Cell Lung Cancer Sensitive to First-Line Chemotherapy</td>
<td>completed</td>
<td>NCT00319969</td>
<td>September 28, 2009</td>
</tr>
</tbody>
</table>

### EXISTING GUIDELINES

<table>
<thead>
<tr>
<th>Publishing Group</th>
<th>Recommendation</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Comprehensive Cancer Network</td>
<td>Small cell lung cancer remains one of the more frustrating malignancies for oncologists to treat. Although responses to initial platinum-based chemotherapy are high, most are not durable, and many patients are candidates for further palliative chemotherapy. Therapeutic options include reinduction or single-agent chemotherapy, depending on the duration of response to front-line treatment. Topotecan is the only approved agent for patients with relapsed disease. Several phase II studies have</td>
<td>Schneider BJ. Management of recurrent small cell lung cancer. JNCCN Journal of the National Comprehensive Cancer Network. 2008;6(3):323-31.</td>
</tr>
</tbody>
</table>
shown a modest benefit with other agents used today, although combination chemotherapy should be avoided because of increased toxicity. Palliative care should always be the focus, especially in patients with recurrent or chemorefractory small cell lung cancer and a poor performance status.

<table>
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<tbody>
<tr>
<td>ESMO</td>
<td>Relapsing patients should be considered for second-line chemotherapy because survival benefits and quality of life benefits have been shown. Candidates for second-line chemotherapy should be selected on the basis of response to first-line therapy, time interval since the discontinuation of first-line therapy, residual toxicity to first-line therapy and performance status, as the likelihood of response to second-line chemotherapy is dependent on these factors. Candidates with low likelihood of benefit from chemotherapy should be considered for palliative radiation therapy. No specific chemotherapy regimen is recommended as studies have not proven superior efficacy or effectiveness.</td>
<td>Sorensen M, Pijs-Johannesma M, Felip E. Small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2010;21(SUPPL. 5):v120-v5</td>
</tr>
<tr>
<td>SEOM clinical guidelines for the treatment of small-cell lung cancer</td>
<td>Sensitive disease, 3-6 months time to progression: First recommended option should be topotecan. Alternatively, an anthracycline-based scheme (if the patient received platinum in the first line) could be used (or vice versa). — Sensitive disease with time free of progression over 6 months: repeat first-line scheme. — Resistant or refractory disease. Topotecan monotherapy is the only clinical recommendation but participation in clinical trials should be encouraged.</td>
<td>Artal Cortes A, Domine Gomez M, Font Pous A, Garcia Campelo R, Cobo Dolls M, Isla Casado D. SEOM clinical guidelines for the treatment of small-cell lung cancer. Clinical and Translational Oncology. 2010;12(1):27-31</td>
</tr>
</tbody>
</table>
Patients relapsed from a response to first-line chemotherapy should be considered for second-line chemotherapy

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:

   1. NO

   If Yes, the document will be immediately removed from the PEBC website, and a note as to its status put in its place. Go to 2.

2. On initial review,
   a. Does the newly identified evidence support the existing recommendations?
   b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?

   Answer Yes or No to each, and explain if necessary:

   2. Yes to both questions

   There is nothing new in the management of extensive stage relapsed small cell lung cancer. Published data does not show any superior chemotherapy regimens beyond what we already know.

   If both are Yes, the document can be ENDORSED. If either is No, go to 3.

3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:

   3. NOT APPLICABLE

   If Yes, a final decision can be DELAYED up to one year. If No, go to 4.

4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?

   4. NOT APPLICABLE

   If Yes, the document needs an UPDATE. It can be listed on the website as IN REVIEW for one year. If a full update is not started within the year, it will be automatically ARCHIVED. If NO, go to 5.

5. If Q2, Q3, and Q4 were all answered NO, this document should be ARCHIVED with no further action.

**Review Outcome** ENDORSE

**DSG/GDG Approval Date** December 11, 2012

**DSG/GDG Commentary** NA

**New References Identified:**


**Search Strategy:**

**EMBASE:**

1. (exp meta analysis/ or exp systematic review/).
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative syntheses or quantitative overview$).tw.
4. (systematic adj (review$ or overview$)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or Jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. 6 or 7
10. (cochrane or Embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliography$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/.
13. randomization/ or single blind procedure/ or double blind procedure/.
14. (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/13-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/.
17. 16 and randomized$.
18. (clinical$ adj trial$).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$ or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. Animal/
33. Human/
34. 32 not 33
35. 31 not 34
36. small-cell lung cancer/
37. small cell lung cancer/
38. lung neoplasms/
39. or/36-38
40. (local neoplasm recurrence or recurrence).mp.
41. (antineoplastic agents or drug therapy or salvage therapy).mp.
42. or/40-41
43. (small cell lung cancer or relapse or recur or refractory or second-line or salvage or rechallenge or retreat or reinduct).tw.
44. 39 and 42 and 43
46. 44 and 45
47. remove duplicates from 46

MEDLINE:
1. meta-Analysis as topic.mp.
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthesis? or quantitative overview?).tw.
5. (systematic adj (review$ or overview$)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psyclit or psyclit or psychinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliography or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinical adj trial$1).tw.
24. (singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. Animal/
38. Human/
39. 37 not 38
40. 36 not 39
41. exp small cell lung carcinoma/
42. lung neoplasms.tw.
43. or/41-42
44. (local neoplasm recurrence or recurrence).mp.
45. (antineoplastic agents or drug therapy or salvage therapy).mp.
46. or/44-45
47. (small cell lung or relapse or recur or refractory or second-line or salvage or rechallenge or retreat or reinduct).tw.
48. 43 and 46 and 47
50. 48 and 49
51. remove duplicates from 50

ASCO:
"small-cell lung cancer" AND ("relapse" OR "recurrent") AND "chemotherapy"
ClinicalTrials.Guv:
"small-cell lung cancer" AND ("relapse" OR "recurrent") AND "chemotherapy"

OUTCOMES DEFINITIONS

1. ARCHIVED - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase "ARCHIVED".

2. ENDORSED - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. DELAY - A Delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. UPDATE - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.