SMALL CELL LUNG CANCER: EXTENSIVE STAGE

Effective date: July, 2012

The recommendations contained in this guideline are a consensus of the Alberta Provincial Thoracic Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Lung cancer is the overall leading cause of cancer mortality in Canadian men and women. By the end of 2012, an estimated 25,600 new cases of lung cancer will be diagnosed in Canada.[1] In addition, an estimated 20,100 Canadian men and women will die from their disease; a total higher than the estimated deaths from prostate, breast, and colorectal cancers combined.[1] The economic impact of lung cancer care is equally as staggering: the mean cost associated with the care of each patient diagnosed with lung cancer in Alberta is reported to be $15,350 for non-small cell lung cancer and $18,243 for small cell lung cancer, not including end-of-life care.[2] Smoking remains the largest single risk factor for lung cancer, responsible for 90 percent of lung cancers in men and 80 percent of lung cancers in women in Canada. Exposure to specific industrial and atmospheric pollutants, including second-hand tobacco smoke, also increases an individual's risk of lung cancer.

Lung cancer can be classified into non-small cell lung cancer (NSCLC) or small-cell lung cancer (SCLC). SCLC accounts for 13 to 20 percent of all lung cancers, with incidence rates reportedly declining for men but continuing to increase for women in most countries. [3,4] SCLC is distinguished from NSCLC by its rapid growth rate, early metastasis to regional lymph nodes and/or distant sites, and its initial sensitivity to chemotherapy and radiotherapy. [3-5] SCLC is most commonly staged using a two-tiered system developed by the Veteran's Administration Lung Cancer Study Group. In this system, patients with limited-stage disease have involvement limited to one hemithorax, regional mediastinal lymph nodes, and ipsilateral supraclavicular lymph nodes. Limited disease can be encompassed within a safe radiation treatment plan, and patients with limited disease therefore are treated with curative intent. [3,6] Patients with extensive-stage SCLC have disease beyond ipsilalteral hemithorax which may include malignant pleural or pericardial effusions or hematogenous metastases.[3] The tumour-node-metastasis (TNM) staging system is less frequently used in SCLC because this system relies on surgical confirmation for accuracy and, apart from a very select group of patients with very early limited disease, patients with SCLC seldom present at a stage for which surgery is appropriate. [4] Nevertheless, the Seventh Edition of the Cancer Staging Manual [7] is now applicable to SCLC as well as NSCLC.

GUIDELINE QUESTIONS

- What are the recommended treatment options for patients with extensive stage small cell lung cancer?

DEVELOPMENT

This guideline was reviewed and endorsed by the Alberta Provincial Thoracic Tumour Team. Members of the Alberta Provincial Thoracic Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Thoracic Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

This guideline was originally developed in July, 2008.

SEARCH STRATEGY

For this guideline update, a search for new or updated practice guidelines published since January 2008 was conducted by accessing the websites of the following organizations: Cancer Care Ontario (CCO), British Columbia Cancer Agency (BCCA), Cancer Care Nova Scotia (CCNS), the National Comprehensive Cancer Network (NCCN), the Scottish Intercollegiate Guidelines Network (SIGN), the National Institute for Health and Clinical Excellence (NICE), the American College of Chest Physicians (ACCP), the Australian Cancer Network, and the European Society for Medical Oncology (ESMO).

Medical journal articles were searched using Medline Ovid, Cochrane Database of Systematic Reviews, and PubMed electronic databases. On PubMed, the search term “extensive stage small cell lung cancer” was used and related terms were included in the search. On Medline and Cochrane, “small cell lung cancer” [MeSH term] with subheadings “drug therapy”, “radiotherapy”, “therapy” and “surgery” was used. Limits selected in both searches included: publication in the last five years, “meta-analysis”, “clinical trial”, “randomized controlled trial”(Medline)/”controlled clinical trial”(PubMed), “clinical trial, phase III”, “clinical trial, phase IV” and “comparative study” (PubMed). Results were further excluded if they were not related to treatment, did not report survival outcomes, or were not phase III or phase IV clinical trials. Another search of Medline was done using the term “small cell lung carcinoma” [MeSH term] with “drug therapy” (subheading) combined with “topotecan” to identify literature related to second-line therapy.

TARGET POPULATION

The recommendations in this guideline apply to adult patients over the age of 18 years.

RECOMMENDATIONS

1. Whenever possible patients should be considered for eligibility in ongoing clinical trials.
2. Patients with extensive stage disease should receive between four and six cycles of platinum-based combination chemotherapy.
    - Cisplatin plus etoposide is the preferred regimen but in patients who are frail or have significant hearing loss, peripheral neuropathy, decreased heart function or have abnormal renal function, carboplatin plus etoposide could be used.
3. Patients with extensive stage SCLC who have achieved at least stable disease after primary treatment should be offered prophylactic cranial irradiation.
4. If progressive disease occurs after more than three months of response to first line chemotherapy, second line chemotherapy is recommended. Cisplatin-etoposide is the preferred option, followed by topotecan or cyclophosphamide, doxorubicin and vincristine (CAV). For those patients with progressive disease less than 3 months from the completion of first line chemotherapy, the cancer should be considered chemo-resistant. Second-line therapy is ineffective. Clinical trials, if available, should be considered.
5. Thoracic irradiation as primary treatment is not routinely recommended for patients with extensive stage SCLC. However, radiotherapy can be used for symptom control where appropriate.

DISCUSSION

Combination Chemotherapy

It is well established that combination chemotherapy is the most effective means of improving overall survival in patients with extensive-stage SCLC, and that platinum-based regimens appear to be more effective than non-platinum containing combinations. In a large meta-analysis of 19 randomized trials involving 4054 patients, Pujol et al. (2000) reported that cisplatin-containing regimens were associated with an increased response rate (OR=1.35; 95% CI 0.69-0.93, p=.00005), as well as a significant reduction in the risk of death at six months (68% versus 66%, OR=0.87; 95% CI 0.75-0.98, p=.002) and one year (29% versus 24%, OR=0.80; 95%CI 0.69-0.93,p=.002) when compared with non-cisplatin based combinations.[8] Four to six cycles of platinum-based chemotherapy for the treatment of extensive stage SCLC is also recommended by the ACCP, NICE and ESMO.[3,9,10]

Recent trials [11-13] have compared cisplatin or carboplatin and etoposide with cisplatin or carboplatin and irinotecan and have found no statistically significant difference in terms of overall survival (OS) or progression-free survival (PFS) between the two regimens. A meta-analysis of randomized controlled trials comparing irinotecan/platinum (IP) with etoposide/platinum (EP) conducted by Jiang et al. (2010) suggests that IP may be likely to prolong OS in patients with previously untreated extensive stage SCLC (HR=0.81, 95% CI=0.66-0.99, p=044).[14] However, pooled hazard ratios for PFS failed to display a difference between IP and EP regimens (HR=0.82, 95% CI=0.64-1.06,P=0.136). The analysis further concluded that IP regimens led to less grade 3-4 anemia, neutropenia and thrombocytopenia than EP regimens, whereas EP led to less grade 3-4 vomiting and diarrhea than IP regimens.[14] A recent meta-analysis by Rossi et al. (2012) compared the outcomes of patients who received carboplatin-based versus cisplatin-based chemotherapy. Median overall survival and progression free survival was comparable between groups (Carboplatin OS= 9.4 months, PFS=5.3 months versus Cisplatin OS=9.6 months, PFS=5.5 months).[15] However, the toxicity profiles were significantly different in each arm, with hematologic toxicity higher with carboplatin and nonhematologic toxicity higher with cisplatin.[15]

A phase III trial compared cisplatin-etoposide (EP) and paclitaxel-cisplatin-etoposide (PET) as first line treatment for extensive disease SCLC. Median overall survival time did not differ between the two arms (EP 9.9 months; PET 10.6 months, p=0.169). However, toxicity-related deaths were 6.5% in the PET arm and 2.4% in the EP arm.[16]

Prophylactic Cranial Irradiation

Metastasis to the brain is a particularly frequent problem in patients with SCLC. There is increasing evidence that prophylactic cranial irradiation (PCI) substantially reduces the risk of brain metastases from SCLC and prolongs disease-free and overall survival.[17,18] In a phase III study conducted by the EORTC, 286 patients with extensive stage SCLC were randomized to undergo either PCI or no further therapy.[18] PCI was associated with a lower cumulative risk of brain metastases at one year when compared with no treatment (14.6% versus 40.4%, HR=0.27; 95% CI 0.16-0.44, p<.001), increased median disease-free survival (14.7 weeks versus 12.0 weeks), as well as increased median overall survival (6.7 months versus 5.4 months). The one-year survival rate was 27.1% (95% CI 19.4-35.5) in the PCI group and 13.3% (95% CI 8.1-19.9) in the no treatment group. Side effects associated with PCI in this study included headache, nausea and vomiting, and fatigue.[18] Patients with extensive stage SCLC who have achieved at least stable disease after primary treatment should be offered prophylactic cranial irradiation (recommendation #3).

The optimal dose of PCI in extensive stage disease has yet to be determined. The meta-analysis by the Prophylactic Cranial Irradiation Overview Collaborative Group (2009) found that effect on survival did not differ significantly with differential PCI doses (groups compared: 8 Gy, 24-25 Gy, 30 Gy, 36-40 Gy), but risks of brain metastases decreased with higher doses. Furthermore, the group found a trend (p=.01) for decrease in brain metastasis risk in favour of earlier administration of PCI after initiation of induction therapy. [17] However, a majority of the trials included in the meta-analysis are of patients with limited stage SCLC, so the applicability of these results in the case of extensive stage should be interpreted with caution.

Thoracic Irradiation

Thoracic irradiation is not routinely recommended for extensive stage SCLC. Several of the guidelines included in this review do however suggest that thoracic irradiation could be considered if there has been a complete response at distant sites and at least a good partial response within the thorax.[3,10] A single institution randomized controlled trial by Jeremic et al.(1999) suggests that the addition of concurrent RT improves survival in patients with extensive stage SCLC that has responded to an initial three cycles of EP chemotherapy with a complete response outside the thorax and at least a partial response in the thorax.[19] However, this is low level evidence and the benefits and risks associated with thoracic irradiation need to be further addressed in randomized trials. The Alberta Provincial Thoracic Malignancy Tumour Team recommends that patients be enrolled in clinical trials whenever feasible. Tumour team members also agree that radiotherapy plays an important role in the palliation of symptoms of metastatic disease, particularly brain, bone, and spinal metastases, as well as superior vena cava syndrome. For a more in-depth review, please refer to the Palliative Radiotherapy Guideline.

Second Line Therapy

If progressive disease occurs after more than three months of response to first line chemotherapy, second line chemotherapy is recommended. Cisplatin-etoposide is the preferred option, followed by topotecan or cyclophosphamide, doxorubicin and vincristine (CAV) (recommendation #4). Although small cell lung cancer is initially chemosensitive, relapse is common.[20] Despite high initial response, the majority of SCLC patients require salvage therapy for disease progression within several months after front line therapy.[21] Median survival is 2-3 months for patients who do not received second-line therapy.[22] Owonikoko et al. (2012) and Cheng et al. (2007) both recommend that patients with sensitive disease and relapse should be re-treated with a platinum/etoposide regimen.[21,22] However, for those patients with progressive disease less than 3 months from the completion of first line chemotherapy, the cancer should be considered chemo-resistant. Second-line therapy is ineffective. Clinical trials, if available, should be considered.

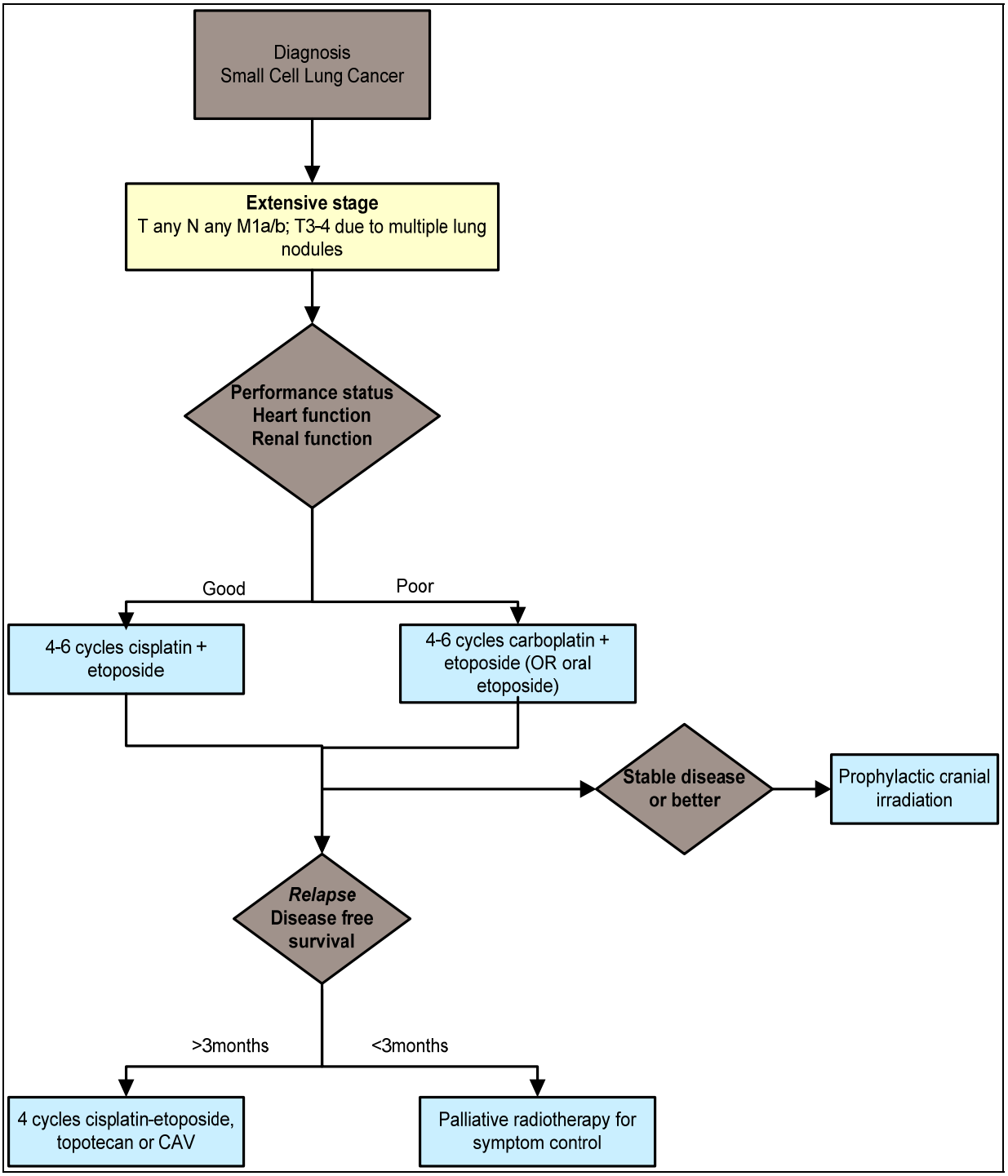
The meta-analysis by Owonikoko et al. (2012) of second-line chemotherapy in sensitive and resistant/refractory SCLC demonstrated an overall response rate of 17.9%; 27% in patients with sensitive disease (progression after > 90 days) and 14.8% for resistant/refractory patients (progression after < 90 days). Furthermore, overall median survival following second-line treatment was 6.7 months; 7.73 months weighted average for sensitive SCLC and 5.45 months for resistant/refractory disease.[21] In the systematic review by Cheng et al. (2007), none of the trials examining different second-line chemotherapy regimens detected a statistically significant difference in tumour response or survival between treatment arms.[22] A retrospective study by Froeschl et al. (2008) of specifically extensive stage SCLC patients who had received second-line therapy found that patients lived longer from the time of relapse (5.2 months versus 1.5 months for those who did not received second-line).[23] However, those chosen to receive therapy were

younger and fitter and only 28% of those who received first-line therapy for extensive disease received second-line, in many cases due to the fact that patients either refused the treatment or were too unwell/died before treatment.[23]

Topotecan and best supportive care has been demonstrated as superior to best supportive care alone in a phase III trial.[24] Patients in this study had relapsed SCLC and were randomized to either best supportive care (n=70) or oral topotecan and best supportive care (n=71). The intent-to-treat analysis found that median overall survival was significantly longer in the topotecan group (25.9 weeks versus 13.9 weeks).[24] Patients within this study were considered unsuitable for IV-delivered topotecan. However, another phase III study suggests that oral topotecan demonstrates activity and tolerability similar to IV topotecan. [25] The response rate for those who received oral topotecan was 18.3% (95% CI 12.2%-24.4%) and 21.9% (95% CI 15.3%-28.5%) for those who received IV topotecan. Median survival was 33 weeks in the oral group and 35 weeks among patients who received IV.[25] A phase II trial also found similar efficacy between IV and oral topotecan.[26]

Von Pawel et al. (1999) conducted a phase III trial comparing CAV with IV topotecan in SCLC patients with progression after 60 or more days.[27] Response rates were 18.3% in the CAV arm versus 24.3% in the topotecan group (p=0.285). Median overall survival was 24.7 months in the CAV arm and 25.0 months with topotecan, and was also not statistically significant (p=0.795).[27] Nevertheless, patients in the CAV arm had lower rates of grade 3-4 thrombocytopenia (15% versus 58%) and anemia (20 % versus 42%).[27]

Figure 1. Algorithm for the management of extensive-stage small cell lung cancer



GLOSSARY OF ABBREVIATIONS

Acronym	Description
ACCP	American College of Chest Physicians
CI	Confidence Interval
EORTC	European Organization for Research and Treatment of Cancer
EP	Etoposide/platinum
ESMO	European Society for Medical Oncology
HR	Hazard ratio
IP	Irinotecan/platinum
NICE	National Institute for Health and Clinical Excellence
NSCLC	Non-small cell lung cancer
OR	Overall response
OS	Overall survival
PCI	Prophylactic Cranial Irradiation
PFS	Progression-free survival
SCLC	Small cell lung cancer

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of Alberta Health Services, Cancer Care.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Thoracic Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services – Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Thoracic Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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