SMALL CELL LUNG CANCER: EXTENSIVE STAGE

Date Developed: July, 2008

Date Revised: September, 2009

The recommendations contained in this guideline are a consensus of the Alberta Provincial Thoracic Malignancy 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 2009, an estimated 23,400 new cases of lung cancer will be diagnosed in Canada.[1] In addition, an estimated 20,500 Canadian men and women will die from their disease, a total higher than the estimated deaths from prostate, breast, and colorectal cancers combined.[1] Despite many research and clinical advances in lung cancer treatments, the age-standardized five-year survival rate for lung cancer is only 15 percent for Canada overall, and 12 percent for Alberta.[1] 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.[2,3] 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.[2-4] SCLC is most commonly staged using a two-tiered system developed by the Veteran's Administration Lung Cancer Study Group. In this staging 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.[2,4] Patients with extensive-stage disease have overt metastatic disease that is identified through imaging or physical examination.[2] 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.[3] Nevertheless, the International Association for the Study of Lung Cancer (IASLC) has recently argued that the proposals made for the forthcoming seventh edition of the TNM seem to be of relevance for SCLC as well.[3]

GUIDELINE GOALS AND OBJECTIVES

- To outline the management recommendations for patients with extensive stage small cell lung cancer.

GUIDELINE QUESTIONS

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

DEVELOPMENT PANEL

This updated ***guideline*** was reviewed and endorsed by the Alberta Provincial Thoracic Malignancy Tumour Team. Members of the Alberta Provincial Thoracic Malignancy Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Updated ***evidence*** was selected and reviewed by a working group comprised of members from the Alberta Provincial Thoracic Malignancy Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit.

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 (1950 to August Week 1, 2009), EMBASE (1980 to August Week 1, 2009), Cochrane Database of Systematic Reviews (3rd Quarter, 2009), and PubMed electronic databases; the references and bibliographies of articles identified through these searches were scanned for additional sources. The search terms included: Lung Neoplasms [MeSH heading], Carcinoma, Small Cell Lung [MeSH heading], practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. Articles were excluded from the final review if they: had a non-English abstract, were not available through the library system, or were published prior to January 2008.

This guideline was developed using the ADAPTE framework as a guide.[4] Recommendations from published guidelines covering treatment for limited stage small cell lung cancer were assembled into a recommendation matrix by a methodologist. All recommendations were systematically reviewed for currency and acceptability for inclusion by two team members: one surgeon and one medical oncologist. A draft guideline was then developed and circulated to the entire Provincial Tumour Team for feedback and approval.

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 decreased heart function or have abnormal renal function, carboplatin plus etoposide could be used.
3. Patients who have achieved at least stable disease after platinum-etoposide should have a discussion with their radiation oncologist regarding the risks and benefits of prophylactic cranial irradiation (PCI).
4. Thoracic irradiation as primary treatment is not routinely recommended for patients with extensive stage SCLC; however, irradiation could be used for symptom control where appropriate.

DISCUSSION

There was a general consensus on how to manage limited stage SCLC amongst the published guidelines included in this updated review. The recommendations contained in this guideline were developed based on local practice and expertise but are consistent with the current literature and guidelines from other cancer care organizations.

Combination Chemotherapy

It is well established that combination chemotherapy is the most effective means of improving 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.* reported that cisplatin-containing regimens were associated with an increased response rate (OR=1.35; 95% CI 0.69-0.93, $p<10^{-5}$), 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 to non-cisplatin based combinations.[5] Etoposide plus cisplatin is the most commonly recommended combination treatment amongst the guidelines included in this review, although etoposide plus carboplatin is a suitable alternative for patients unable to tolerate cisplatin. The Alberta Provincial Thoracic Malignancy Tumour Team has adapted the recommendations from the published guidelines of the ACCP, NICE, Australian Cancer Network, and ESMO, which all state that patients with extensive stage disease should receive between four and six cycles of platinum-based combination chemotherapy, and there is not sufficient evidence to support continuing treatment beyond six cycles.[2,6-8]

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.[9,10] In a recent phase III study conducted by the EORTC, 286 patients with extensive stage disease were randomized to undergo either PCI or no further therapy.[9] 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 increase overall survival 6.7 months versus 5.4 months).[9] 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. Based on these promising results, the Alberta Provincial Thoracic Malignancy Tumour Team recommends that patients with extensive stage SCLC who have achieved *at least stable disea*se after platinum plus etoposide combination chemotherapy should have a discussion with their radiation oncologist regarding the risks and benefits of PCI (recommendation #3).

The optimal dose of PCI in extensive stage disease has yet to be determined. However, the CCO guideline on PCI recommends that shorter schedules are preferable.[11] The schedule recommended by the Alberta Provincial Thoracic Malignancy Tumour Team is between 20 Gy/ 5 fractions and 30 Gy/ 10 fractions, at the discretion of the radiation oncologist.

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.[2,6,12] The benefits and risks associated with thoracic irradiation need to be further addressed in randomized trials; therefore 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 Guidelines.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
ACCP	American College of Chest Physicians
CCO	Cancer Care Ontario
CI	confidence interval
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
HR	hazard ratio
IASLC	International Association for the Study of Lung Cancer
NICE	National Institute for Health and Clinical Excellence
NSCLC	non-small cell lung cancer
OR	odds ratio
PCI	prophylactic cranial irradiation
SCLC	small cell lung cancer
TNM	tumour-node-metastasis

IMPLEMENTATION STRATEGY

- Present the guideline in the tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.

EVALUATION STRATEGY

A formal review will be conducted in 2010, however if new evidence is brought forward before that time, the guideline will be changed accordingly.

DECLARATION OF CONFLICT OF INTEREST

None of the authors of this guideline had any conflict of interest related to evidence or recommendations in this guideline.

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