Evidence-based Series 7-13-1 Version 2

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

The Role of Combination Chemotherapy in the Initial Management of Limited-Stage Small-Cell Lung Cancer

Members of the Lung Cancer Disease Site Group

An assessment conducted in December 2015 deferred the review of Evidence-based Series (EBS) 7-13-1 Version 2, which means that the document remains current until it is assessed again next year. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol)

This document, which is available on the CCO Website, is comprised of the following 3 sections:

Section 1: Summary (ENDORSED)
Section 2: Systematic Review
Section 3: Guideline Review Summary

Release Date: October 5, 2012

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Guideline Report History

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Evidence-based Series 7-13-1 Version 2: Section 1

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

The Role of Combination Chemotherapy in the Initial Management of Limited-Stage Small-Cell Lung Cancer: Guideline Recommendations

S.A. Laurie, D. Logan, B.R. Markman, J.A. Mackay, W.K. Evans
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 3: Document Summary and Review Tool for a summary of updated evidence published between 2003 and 2012 and for details on how this Clinical Practice Guideline was ENDORSED.

Report Date: October 5, 2012

Guideline Question

For patients with limited-stage small-cell carcinoma of the lung, what is the optimal combination chemotherapy regimen, schedule of administration and duration of therapy for first-line treatment?

Target Population

These recommendations apply to adult patients with limited-stage small cell lung cancer.

Recommendations

- **Update**
  Etoposide-cisplatin is the preferred regimen for adult patients with limited-stage small-cell lung cancer who are being treated with combined-modality therapy with curative intent.

- **Update**
  It is acceptable to offer the alternation of etoposide-cisplatin with cyclophosphamide-doxorubicin-vincristine; however, if this regimen is used, locoregional radiotherapy should not be delivered concurrently with an anthracycline.

- **Update**
  Standard chemotherapy doses should be used. The doses and schedules of administration of these recommended chemotherapy regimens are detailed in Appendix 1 of the full guideline report. The evidence does not support the routine use of dose-intensive regimens.
Qualifying Statements

- **Update**
  If bolus etoposide-cisplatin is selected as the treatment of choice, there is evidence from one randomized trial that the optimal sequence of administration of the components of the regimen is cisplatin followed by etoposide. The total dose of etoposide per cycle of chemotherapy should be administered in divided doses given daily over three to five days.

- **Update**
  The optimal duration of chemotherapy treatment is uncertain. There is insufficient evidence to recommend a specific number of treatment cycles. There is no evidence that maintenance chemotherapy (i.e., chemotherapy beyond six cycles provided to patients who have shown a response to the original chemotherapeutic regimen) prolongs survival, and, therefore, a maximum of six cycles is recommended.

- **Update**
  Although carboplatin is commonly substituted for cisplatin in the etoposide-cisplatin combination, there are insufficient data from clinical trials to support this substitution in patients with limited small-cell lung cancer being treated with curative intent.

- **Update**
  Only 10 trials of the 50 trials reviewed in this guideline focused exclusively on limited-stage disease, and, in the remaining trials, the number of patients with limited-stage disease was generally small. The evidence for an optimal chemotherapy regimen for this patient population must be interpreted in light of these limitations.

Methods

Entries to MEDLINE (1985 through December 2003), CANCERLIT (1985 through October 2002) and the Cochrane Library (2003, Issue 4) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology for 1990 through 2003 were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by three members of the Practice Guidelines Initiative’s Lung Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Lung Cancer Disease Site Group, which comprises medical and radiation oncologists, pathologists, surgeons, a medical sociologist and two patient representatives.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the practice guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- **Update**
  Fifty randomized trials met the guideline inclusion criteria, including 21 trials that directly compared at least two different chemotherapy regimens for the treatment of small-cell lung cancer and 14 trials that compared a dose-intensive chemotherapy regimen with a standard regimen.

- **Update**
  Thirteen trials compared one of the two most commonly used regimens, etoposide-cisplatin and cyclophosphamide-doxorubicin-vincristine, with another chemotherapy
regimen. None of the other combination regimens was conclusively shown to be superior to either cyclophosphamide-doxorubicin-vincristine or etoposide-cisplatin alone.

- **Update**
  Variations of the two most commonly used regimens were directly compared in three randomized trials, with crossover to the opposite regimen recommended for non-responding or progressing disease. Two trials compared cyclophosphamide-doxorubicin-vincristine with etoposide combined with a platinum agent (cisplatin in one trial, carboplatin in the other) and reported no survival differences between treatments, although toxicity was generally more frequent with the anthracycline regimen. However, in the trial that included cisplatin, more patients receiving the anthracycline-based regimen did not respond and were crossed-over to etoposide-cisplatin, which may have masked any differential treatment effect. The largest and most recent trial, involving a subgroup of 214 limited-disease patients, compared etoposide-cisplatin with cyclophosphamide-epirubicin-vincristine and detected a significant survival benefit in favour of etoposide-cisplatin (median, 14.5 versus 9.7 months; p=0.001 log rank). Patients in this trial also received thoracic radiotherapy concurrently with cycle three of chemotherapy. Toxicity data for the two regimens were not reported.

- **Update**
  Two meta-analyses examined the role of cisplatin- or etoposide-based chemotherapy regimens in the treatment of small-cell lung cancer. Both analyses included only published data and did not obtain individual patient data. Neither meta-analysis reported results separately for limited-stage disease, and there was considerable overlap among the trials included in each meta-analysis. One of the meta-analyses included 4,054 patients from 19 trials and detected a significant survival benefit at one year in favour of cisplatin-containing regimens (odds ratio, 0.80; 95% confidence interval, 0.69 to 0.93; p=0.002). This corresponded to a 4.4% increase in the probability of survival at one year. The second meta-analysis included 7,173 patients from 36 trials and detected a significant survival advantage for etoposide-based regimens, with or without cisplatin, compared with regimens containing neither of these chemotherapeutic agents. The corresponding mortality hazard ratios were 0.57 with cisplatin (95% confidence interval, 0.51 to 0.64, p=0.001) and 0.72 without cisplatin (95% confidence interval, 0.67 to 0.78, p<0.001). Superior survival was also detected for etoposide-cisplatin-containing regimens compared with etoposide- or teniposide-based regimens without cisplatin (mortality hazard ratio 0.74, 95% confidence interval, 0.66 to 0.83, p<0.001).

- There is conflicting evidence concerning a survival advantage for a regimen that alternates etoposide-cisplatin with cyclophosphamide-doxorubicin-vincristine compared with either regimen alone.

- **Update**
  Among the 14 randomized trials that compared a dose-intensive with a standard chemotherapy regimen, the data are conflicting with no consistent advantage evident for the dose-intensity treatment approach.

**Related Guidelines**
Practice Guidelines Initiative’s Practice Guideline Reports:

- #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.*
**Updating**
This document will be reviewed in three years time to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. The outcome of the review will be posted on the CCO website. If new evidence that will result in changes to these recommendations becomes available before three years have elapsed, an update will be initiated as soon as possible.

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