Complete Summary

GUIDELINE TITLE

The role of combination chemotherapy in the initial management of limited-stage small-cell lung cancer.

BIBLIOGRAPHIC SOURCE(S)

Lung Cancer Disease Site Group. Laurie SA, Logan D, Markman BR, Mackay JA, Evans WK. The role of combination chemotherapy in the initial management of limited-stage small-cell lung cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Dec [online update]. 51 p. (Practice guideline report; no. 7-13-1). [75 references]

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SCOPE

DISEASE/CONDITION(S)

Limited-stage small-cell carcinoma of the lung

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Pulmonary Medicine
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the optimal combination chemotherapy regimen, schedule of administration, and duration of therapy for first-line treatment in patients with limited-stage small-cell carcinoma of the lung

TARGET POPULATION

Adult patients with limited-stage small-cell lung cancer

INTERVENTIONS AND PRACTICES CONSIDERED

Combination chemotherapy regimens compared with etoposide-cisplatin (EP) and cyclophosphamide-Adriamycin (doxorubicin)-vincristine (CAV)

1. etoposide-carboplatin
2. etoposide-cisplatin-ifosfamide
3. cyclophosphamide-Adriamycin-etoposide
4. cyclophosphamide-Adriamycin-vincristine-etoposide
5. cyclophosphamide-etoposide-vincristine
6. Adriamycin-vincristine-etoposide

MAJOR OUTCOMES CONSIDERED

Survival was the primary outcome of interest. Adverse effects were also considered.

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Original Guideline: March 2001

A systematic search of MEDLINE (Ovid) and CANCERLIT (Ovid) databases (1985 through October 2000) was carried out. "Carcinoma, small-cell" (medical subject heading [MeSH] and text word) were combined with "chemotherapy, adjuvant" (MeSH), "drug therapy" (MeSH), "antineoplastic agents, combined" (MeSH) and "chemotherapy" (text word). These terms were then combined with the search terms for the following study designs: practice guidelines, meta-analyses, systematic reviews, and randomized controlled trials. Searches of the Cochrane Library database (2000, Issue 3) and personal reprint files were also conducted. The Physician Data Query (PDQ) clinical trials database on the Internet

http://www.cancer.gov/search/clinical_trials/ and the proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO) for 1990 through 2000 were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from these sources, as well as from review articles on small-cell lung cancer, were searched for additional trials.

December 2003 Update

The original literature search has been updated using MEDLINE (through December 2003), CANCERLIT (through October 2002), the Cochrane Library (Issue 4, 2003), and the proceedings of the annual meetings of the American Society of Clinical Oncology (2001 through 2003).

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. Randomized controlled trials comparing combination chemotherapeutic regimens, duration of chemotherapy, or schedules of chemotherapy for the first-line treatment of patients with limited-stage small-cell lung cancer (SCLC)
2. Abstracts of trials were considered.

Exclusion Criteria

1. Phase I and II studies were not considered for inclusion in this report because of the availability of randomized controlled trials.
2. Trials were excluded if data for patients with limited-stage disease were not reported separately from data for patients with extensive-stage SCLC.
3. Trials were excluded if survival data for patients with limited-stage SCLC were not available and reported separately from patients with extensive-stage SCLC.
4. Trials that used chemotherapy regimens containing procarbazine and/or lomustine or another nitrosourea (e.g., cyclophosphamide-methotrexate-vincristine-lomustine chemotherapy) were not considered. The use of regimens containing these agents has largely been abandoned in North America because of the adverse effects associated with them and because of the availability of other regimens of equal efficacy and reduced toxicity.
5. Studies of palliative chemotherapy were not considered, since the focus of this practice guideline report is chemotherapy with curative intent.
6. Studies of dose intensity (e.g., studies that examined dose-intensive weekly regimens or autologous bone marrow transplant) were not considered. It was the consensus of the Lung Disease Site Group (DSG) that dose-intensity trials should be excluded from this practice guideline report because their results would apply to only a select group of patients.
7. Papers published in a language other than English were not considered.

December 2003 Update

As a result of feedback received during the peer review process, trials of dose-intensive chemotherapy were included in the updated guideline report. Trials that added granulocyte-colony stimulating factor (G-CSF) to one of the treatment arms, but that did not alter the dose or administration schedule of the chemotherapy, were not considered. In addition, meta-analyses that compared different combination chemotherapeutic regimens in the treatment of SCLC were also included in the updated guideline report.

NUMBER OF SOURCE DOCUMENTS

There were 17 randomized trials, two published in abstract form, that compared at least two chemotherapy regimens for small cell lung cancer, six randomized trials of alternating chemotherapy compared with either a non-alternating regimen or a regimen of sequential administration of combination chemotherapy, four randomized trials that compared schedules or routes of administration of etoposide, and five trials of duration of chemotherapy.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

It was decided not to pool the results of all the trials of chemotherapy for limited-stage small-cell lung cancer (SCLC) because the trials were too clinically heterogeneous with respect to patient populations and chemotherapy regimens. The subgroup of trials that compared cyclophosphamide-Adriamycin-vincristine (CAV) chemotherapy with cyclophosphamide-Adriamycin-vincristine-etoposide (CAVE) was sufficiently homogenous to be pooled. Results were pooled using the software package Review Manager 4.1 (Metaview © Update Software). The effect of CAVE compared with CAV is expressed as a risk ratio (RR) with a 95% confidence interval (CI). The risk ratio is the ratio of the risk of death in patients treated with CAVE to the risk of death in patients treated with CAV, with values less than one favouring CAVE and values greater than one favouring CAV.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Original Guideline: March 2001

Members of the Lung Disease Site Group (DSG) felt that the literature that had been reviewed and collated for this guideline was so extensive that it needed to be presented in a very concise format. This was done by using tables to summarize data, with careful attention to avoid duplicating information in the text and the tables. The recommendations were written to clarify that the guideline concerned first-line therapy only. The Lung DSG felt that second-line therapy should be the subject of a separate guideline. As a guideline providing recommendations on the role of radiotherapy in limited small-cell lung cancer had been previously completed, the DSG felt that a reference should be made to this document, as well as to the guideline under development on the role of prophylactic chemotherapy in patients who achieve complete response after therapy for small-cell lung cancer (SCLC). During its deliberations, the members of the Lung DSG had discussed the need to present information on the biological equivalence of cisplatin and carboplatin in small-cell lung cancer. The draft document sent for practitioner feedback made reference to the equivalence of etoposide-cisplatin and etoposide-carboplatin. However, there were no data presented in the document to support a recommendation that these regimens were equivalent; practitioners commented on this lack of supporting evidence. In fact, the only trial that compared these two regimens head-to-head had been removed from an earlier draft because the trial did not report survival data for patients with limited-disease SCLC. This trial by Skarlos et al randomized 143 eligible limited- and extensive-disease SCLC patients to either etoposide-cisplatin or to etoposide-carboplatin; 41 patients with limited disease were randomized to each arm. The overall survival of patients on the two treatment arms was similar, but data on the survival of patients with limited disease were not presented. The trial was clearly underpowered to prove equivalence of the two treatment regimens in either limited or extensive disease. Following further discussion of this trial at a Lung DSG meeting, and in the absence of other data, it was decided to remove the reference that etoposide-carboplatin was biologically equivalent to etoposide-cisplatin from the Recommendation section and to discuss the limited amount of data available on this issue in the Consensus section.

Members of the DSG discussed extensively the issue of the number of treatment cycles that patients with small-cell lung cancer should receive. It was recognized that most of the clinical trials on which the recommendations in this guideline are based used six cycles of chemotherapy. However, the trend in clinical practice increasingly has been to use only four cycles of cisplatinum-based chemotherapy. Lung DSG members felt that a statement acknowledging this difference should be included in the recommendations.

December 2003 Update:

The Lung DSG noted the discrepancy between the original guideline recommendations and current practice in North America, where etoposide-cisplatin (EP) along with concurrent radiation is generally considered optimal treatment for limited-stage SCLC. They also noted that there is evidence for the superiority of EP over cyclophosphamide-adriamycin-vincristine (CAV) in the treatment of extensive-stage SCLC. In reviewing the data from the two meta-analyses and the trial by Sundstrom et al, the DSG agreed that the weight of

evidence supports the use of EP over cyclophosphamide-adriamycin-vincristine, particularly where concurrent radiotherapy will be administered.

The evidence for intensification of the dose of chemotherapy was also discussed. However, although a few individual trials have demonstrated a survival benefit to a dose-intensive regimen over a standard regimen, the data are conflicting, and no clear and consistent advantage exists. The DSG agreed that only selected patients with limited-stage SCLC would be suitable for a dose-intensive approach and, therefore, dose-intensive regimens should only be used in the context of a clinical trial.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 37 medical oncologists in Ontario. 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. Follow-up reminders were sent at approximately two weeks (post card*) and four weeks (complete package mailed again). The Lung Disease Site Group (DSG) reviewed the results of the survey.

These practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Lung DSG and the Practice Guidelines Coordinating Committee.

December 2003 Update

The Lung DSG considered the changes in the guideline recommendations to represent a change in emphasis rather than a substantive change in direction; therefore, the updated guideline and modified recommendations were not circulated for external review.

*This practice-guideline-in-progress report was included in a small study of the effectiveness of reminder post cards in encouraging clinicians to provide practitioner feedback, carried out by the Program in Evidence-Based Care. Practitioners who had not responded to the practitioner feedback survey at

approximately two weeks after the initial mailing were randomly assigned to either a "reminder post card" group who were sent a post card encouraging them to complete the practitioner feedback questionnaire (standard practice in the practitioner feedback process), or a "no reminder post card" group, who did not receive the standard post card. The result was that approximately half of the non-responders were sent post cards at two weeks after the initial mailing.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- 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.
- 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.
- 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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by meta-analyses and randomized trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- 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.
- 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.

- 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.
- 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.

POTENTIAL HARMS

- Adverse effects associated with cyclophosphamide-Adriamycin-vincristine (CAV) are myelosuppression, nausea and vomiting, alopecia, neurotoxicity, and cardiotoxicity. When combined with concurrent thoracic radiotherapy, myelosuppression is increased, and cardiopulmonary toxicities may result. In vitro studies have shown that the combination of etoposide with cisplatin leads to synergistic cytotoxic effects.
- Adverse effects associated with etoposide-cisplatin (EP) include nausea and vomiting, nephrotoxicity, neurotoxicity, ototoxicity, and myelosuppression.
- With respect to adverse effects, cyclophosphamide-Adriamycin-etoposide resulted in greater myelosuppression but less neurotoxicity compared with CAV, cyclophosphamide-etoposide-vincristine produced less cardiotoxicity than CAV, and Adriamycin-vincristine-etoposide resulted in less myelosuppression than CAV.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- 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.
- 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.
- 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.
- 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.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Lung Cancer Disease Site Group. Laurie SA, Logan D, Markman BR, Mackay JA, Evans WK. The role of combination chemotherapy in the initial management of limited-stage small-cell lung cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Dec [online update]. 51 p. (Practice guideline report; no. 7-13-1). [75 references]

ADAPTATION

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

DATE RELEASED

2003 Dec

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Lung Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Lung Disease Site Group (DSG) disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The role of combination chemotherapy in the initial management of limited-stage small-cell lung cancer. Summary. Toronto (ON): Cancer Care Ontario, 2003 Dec. Electronic copies: Available from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on May 14, 2004. The information was verified by the guideline developer on June 2, 2004.

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