



Complete Summary

GUIDELINE TITLE

Chemotherapy in stage IV (metastatic) non-small cell lung cancer.

BIBLIOGRAPHIC SOURCE(S)

Lung Cancer Disease Site Group. Chemotherapy in stage IV (metastatic) non-small cell lung cancer. Toronto (ON): Cancer Care Ontario (CCO); 2005 Jan. 22 p. (Practice guideline report; no. 7-2). [28 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, 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.

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SCOPE

DISEASE/CONDITION(S)

Metastatic (stage IV) non-small cell lung cancer (NSCLC)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate whether chemotherapy improves survival and quality of life in patients with metastatic, stage IV non-small cell lung cancer (NSCLC)

TARGET POPULATION

Adult patients with metastatic, stage IV non-small cell lung cancer (NSCLC)

INTERVENTIONS AND PRACTICES CONSIDERED

Platinum-based chemotherapy (combination regimens containing cisplatin [or its analog, carboplatin])

Note: Non-platinum-based chemotherapy regimens, such as vinorelbine, gemcitabine, paclitaxel, docetaxel, lonidamine, or vindesine, were considered, but not specifically recommended.

MAJOR OUTCOMES CONSIDERED

- Survival
- Quality of life
- Response rate
- Adverse effects of treatment

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
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Original Guideline: February 1996

The electronic databases MEDLINE and CANCERLIT were searched for the years January 1980 to June 1994. Search terms included non-small cell lung cancer, lung neoplasms, stage IV, metastatic, drug therapy, supportive care, clinical trials, research design, meta-analysis, guidelines. Articles identified by the searches, found in personal files, cited in relevant papers, cited in reviews and proceedings of meetings (e.g., American Society of Clinical Oncology) were retrieved and reviewed.

Update: January 2003

The original literature search has been updated using MEDLINE (through January 2003), CANCERLIT (through October 2002), the Cochrane Library (Issue 2, 2002), and the proceedings of the American Society of Clinical Oncology (1997 through 2001).

Inclusion Criteria

Meta-analyses were selected for review as were all randomized controlled trials (RCTs) that compared chemotherapy plus supportive care with supportive care alone for patients with metastatic (stage IV) non-small cell lung cancer (NSCLC). All published material was reviewed, as was material that had been submitted for publication.

NUMBER OF SOURCE DOCUMENTS

Original Guideline: February 1996

Three meta-analyses were reviewed.

Update: January 2002

A meta-analysis and eight randomized controlled trials were reviewed.

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

Original Guideline: February 1996

The guideline report was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) using the methodology of the Practice Guidelines Development Cycle (see the companion document by Browman, et al. (See "Availability of Companion Documents" field.) Evidence was selected and reviewed by members of the Cancer Care Ontario Practice Guidelines Initiative's Lung Cancer Disease Site Group (DSG) and methodologists.

Update: January 2003

The evidence in the original guideline included three meta-analyses that incorporated many of the same trials; therefore, further pooling of data was not appropriate. The trials identified during the update and review process were considered too clinically heterogeneous to pool: two trials involved cisplatin-based combination regimens, one included a carboplatin-based combination regimen, and the remaining five trials included different single-agent chemotherapies.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Original Guideline: February 1996

There was considerable discussion amongst the Lung Disease Site Group (DSG) about the ultimate benefit of treating patients with stage IV non-small cell lung cancer (NSCLC) with chemotherapy. Although the evidence presented in this report does not suggest a long-term (i.e., beyond 1-year) survival benefit for patients receiving chemotherapy, it does suggest there is a clear benefit in the form of a small prolongation in survival (median survival and proportion of patients alive at one year) and in the reduction of disease-related symptoms. Ultimately, it was felt that the treatment a patient receives will vary depending on the goal of the treatment and the outcome that is clinically important for the individual patient.

For patients who value prolonged survival (of the expected magnitude) as the primary goal of their treatment, there is strong evidence that cisplatin-based chemotherapy is the treatment of choice. However, this does not preclude the use of newer chemotherapeutic agents such as vinorelbine (see the Ontario Cancer Treatment Practice Guidelines Initiative's practice guideline *Use of vinorelbine in non-small cell lung cancer*). For patients who value improved quality of life as the primary goal of their treatment, the evidence is less strong that chemotherapy is the treatment of choice. However, it may still be a reasonable treatment option to offer chemotherapy in this scenario as it may reduce symptoms; this may subsequently improve quality of life.

A critical aspect of this recommendation and the deliberations of the group was that physicians *should* enter into a discussion with their patients about the risks and benefits of all treatment options, including the option of chemotherapy (where it is medically appropriate). When patients are fully informed of their

options, the values they hold and choices they make about their treatment should be respected.

The Lung Disease Site Group agreed that the magnitude of the survival prolongation was small and, as such, would not preclude the study of investigational agents in previously untreated patients with stage IV disease. Further investigations that incorporate formal quality of life evaluations are also needed. Finally, as the role of immediate versus delayed treatment with chemotherapy is not clear, clinical trials addressing this issue are warranted.

The cost to the health care system of implementing a recommendation for chemotherapy treatment in stage IV disease was also deliberated. It was recognized that there are currently a variety of chemotherapy regimens that are used as "standard" for which there is only evidence from cohort studies of efficacy. However, these regimens produce response rates and median survival times similar to regimens studied in randomized trials and found superior to best supportive care only.

Update: January 2003

The information above remains current.

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

Original Guideline: February 1996

Practitioner feedback was obtained through a mailed survey of 79 practitioners 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 four weeks (telephone) and six weeks (mail). Results of the survey were reviewed by the Lung Cancer Disease Site Group.

The Coordinating Committee of the Cancer Care Ontario Practice Guidelines Initiative externally evaluated the practice guideline for final approval.

This practice guideline was also reviewed by two external reviewers prior to publication in the journal *Cancer Prevention and Control*.

Update: January 2003

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

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Strong evidence including meta-analyses indicates that there is a small survival benefit of cisplatin-based chemotherapy over best supportive care in patients with non-small cell lung cancer and good performance status.
- If survival is the main outcome of interest for a patient, it is reasonable to offer chemotherapy to medically suitable patients as an option for this condition with a full discussion of the benefits, limitations, and toxicities.
- If symptom control and/or quality of life are the outcomes of interest for a patient, chemotherapy is a reasonable option which may improve quality of life and reduce disease-related symptoms.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Original Guideline: February 1996

There were three published meta-analyses available on this topic.

Update: January 2003

New evidence includes a meta-analysis, and eight randomized controlled trials comparing chemotherapy regimens (three platinum-based and five non-platinum-based) and best supportive care or palliative care with best supportive care or palliative care alone in patients with metastatic stage IV non-small cell lung cancer.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Original Guideline: February 1996

A meta-analysis of individual patient data from 1190 participants in 11 randomized trials found a survival benefit at 1 year for patients treated with chemotherapy plus supportive care (pooled hazard ratio = 0.84; 95% confidence interval (CI), 0.74 to 0.95) compared with those who received supportive care alone. No benefit for patients treated with chemotherapy was found beyond one year. Subgroup analyses suggested a benefit for patients receiving chemotherapy regimens containing cisplatin (pooled hazard ratio = 0.73; 95% CI, 0.63 to 0.85; relative risk reduction for death is 27%; absolute improvement in 1-year survival rate, 10%, 95% CI, 5-18%; gain in median survival, 1.5 months, 95% CI, 1 to 2.5 months). In a subgroup analysis of trials that used long-term alkylating agents other than cisplatin as part of the chemotherapy regimen (an approach no longer used as therapy in non-small cell cancer), the meta-analysis demonstrated a detrimental effect of chemotherapy on survival (pooled hazard ratio, 1.26; 95% CI, 0.96 to 1.66; p=0.09).

Update: January 2003

- Eight randomized trials, published after the meta-analysis described above, add further evidence of a modest survival benefit of chemotherapy over best supportive care in the treatment of advanced non-small cell lung cancer. The chemotherapy regimens varied in the number and types of agents employed; three included cisplatin or its analog, carboplatin. The increase in median survival for platinum-based regimens was consistent with previous reports, ranging from 1.8 to 4.5 months. Seven of the randomized trials included quality of life assessments, which generally showed superiority in overall quality of life and/or specific measures of quality of life in the chemotherapy treated patients compared with those who received only supportive care.
- For non-platinum-based chemotherapy, the increase in median survival was lower but still significant for single-agent vinorelbine or paclitaxel (7 weeks and 8 weeks, respectively), and there was a significant one-year survival advantage for docetaxel over best supportive care (25% vs. 16%). There was no significant effect on survival with single-agent gemcitabine or lonidamine.

POTENTIAL HARMS

Original Guideline: February 1996

The original guideline report did not include information about the adverse effects of chemotherapy.

Update: January 2003

- In a randomized trial comparing two chemotherapy regimens, the main adverse effects experienced by patients were nausea and vomiting and reversible alopecia, which occurred in all patients. Hematological toxicity was more frequently seen in patients treated with best supportive care+IEP (ifosfamide 3 gm/m² with mesna uroprotection, epirubicin 60 mg/m² intravenous on day 1, cisplatin 60 mg/m² IV on day 2) than best supportive care+MVP (mitomycin-C 8 mg/m² IV on day 1, cisplatin 100 mg/m² IV on day 1, vinblastine 4 mg/m² intravenous on days 1, 15); grade 3 and 4 anemia was reported in 28.5% and 15.9 % of patients, grade 3 and 4 leukopenia in

- 7.1% and 7.4% of patients and grade 3 and 4 thrombocytopenia in 7.1% and 7.4% of patients, respectively.
- Among the studies involving non-platinum-based chemotherapy, grade 3 and 4 hematological toxicities occurred with most agents and were common for paclitaxel and docetaxel. Grade 2 to 4 constipation occurred in 21% of patients receiving vinorelbine, grade 3 to 4 infection occurred in approximately 10% of patients receiving paclitaxel or docetaxel, and asthma or myalgia were common with paclitaxel, docetaxel and lonidamine.
 - Myelosuppression, sepsis resulting in hospitalization, drug-specific adverse effects and death were reported as complications of chemotherapy in randomized trials.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The Lung Cancer Disease Site Group agreed that the magnitude of the survival prolongation was small and, as such, would not preclude the study of investigational agents in previously untreated patients with stage IV disease. Further investigations that incorporate formal quality of life evaluations are also needed. Finally, as the role of immediate versus delayed treatment with chemotherapy is not clear, clinical trials addressing this issue are warranted.
- 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

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

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

DATE RELEASED

1996 Feb 14 (revised 2005 Jan)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is 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

Not stated

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Chemotherapy in stage IV (metastatic) non-small cell lung cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2005 Jan. Various p. (Practice guideline; no. 7-2) Electronic copies: Available in Portable Document Format (PDF) 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 summary was completed by ECRI on January 5, 1999. The information was verified by the guideline developer as of February 22, 1999. This NGC summary was updated by ECRI on December 17, 2001. The updated information was verified by the guideline developer as of January 10, 2002. This summary was updated by ECRI on July 5, 2002. The updated information was verified by the guideline developer on August 19, 2002. This NGC summary was updated by ECRI on August 17, 2006. The updated information was verified by the guideline developer on August 23, 2006.

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