



Complete Summary

GUIDELINE TITLE

Chemotherapy for recurrent, metastatic, or persistent cervical cancer: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Hirte H, Strychowsky J, Oliver T, Fung-Kee-Fung M, Elit L, Oza A, Gynecology Cancer Disease Site Group. Chemotherapy for recurrent, metastatic, or persistent cervical cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Jul 5. 21 p. (Evidence-based series; no. 4-20). [27 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)

Recurrent, metastatic, or persistent cervical cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Obstetrics and Gynecology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the front-line chemotherapeutic options for women with recurrent, metastatic, or persistent cervical cancer

TARGET POPULATION

Women with metastatic, recurrent, or persistent cervical cancer for whom first-line treatment with chemotherapy is indicated

INTERVENTIONS AND PRACTICES CONSIDERED

1. Cisplatin plus topotecan
2. Other single-agent or combination chemotherapy regimens as part of randomized trials

MAJOR OUTCOMES CONSIDERED

- Response rate
- Survival
- Toxicity
- Quality of life (QOL)

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

Literature Search Strategy

The literature was searched using MEDLINE (1966 through February 2006), EMBASE (1980 to February 2006), the Cochrane Library (Cochrane Database of Systematic Reviews [2006 Issue 1], and Cochrane Controlled Trials Register

[2006 Issue 1]), the Canadian Medical Association Infobase, and the National Guidelines Clearinghouse. The conference proceedings of the American Society of Clinical Oncology (1995-2005) and the European Society of Medical Oncology (2002-2005) were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed, and the reference lists from these sources and recent review articles were searched for additional trials.

The literature search of the electronic databases combined disease specific terms (cervix neoplasms/ or cervi.mp. and neoplasm.mp. or cancer.mp. and neoplasm metastasis/ or neoplasm recurrence, local/ or metasta.mp. or recurren.mp. or persistent.mp. or advance.mp.) with treatment specific terms (chemotherapy.mp. or drug therapy/) for the following study designs and publication types: randomized controlled trials, practice guidelines, systematic reviews, and meta-analyses. It was determined a priori that the search would be expanded to include other study designs if the search of the literature failed to identify sufficient evidence to inform the evidence-based series.

Study Selection Criteria

Inclusion Criteria

Articles were included in the systematic review of the evidence if they were fully published reports or abstracts and met the following criteria:

1. Randomized controlled trials (RCT) comparing chemotherapy to other chemotherapeutic agents or no further treatment for recurrent, metastatic, or persistent cervical cancer and reporting at least one of the following outcomes: response rate, survival, toxicity, or quality of life (QOL).
2. Randomized controlled trials reporting on heterogeneous populations (e.g., included women with a range of disease stages) if results were given separately for patients with recurrent, metastatic, or persistent cervical cancer. Evidence-based clinical practice guidelines, systematic reviews, or meta-analyses explicitly based on randomized controlled trials were also eligible for inclusion in the systematic review of the evidence.

Exclusion Criteria

Articles were excluded from the systematic review of the evidence if they were:

1. Non-English-language publications
2. Studies evaluating the role of radiotherapy administered with chemotherapy

NUMBER OF SOURCE DOCUMENTS

The literature search identified 15 randomized controlled trials eligible for inclusion in the systematic review of the evidence. Fourteen of the trials were published as full reports, and one was available only in abstract form. Two trials reported quality of life (QOL) data in separate publications.

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

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Combining results across trials provides added power for detecting the efficacy of the treatment and improves the reliability or confidence of the point estimate. Given the clinical heterogeneity of the patient populations and treatment regimens, especially concerning prior radiosensitization with cisplatin in primary therapy, the data were deemed inappropriate for pooling by the Gynecology Cancer Disease Site Group (DSG), and, therefore, meta-analyses were not conducted.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This evidence-based series was developed by the Gynecology Cancer Disease Site Group (DSG) of Cancer Care Ontario's Program in Evidence-Based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on chemotherapy for recurrent, metastatic, or persistent cervical cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Fifteen randomized trials reported outcomes for chemotherapeutic regimens for the treatment of patients with recurrent, metastatic, or persistent cervical cancer. Seven of those trials compared single-agent cisplatin to combination cisplatin-based chemotherapy. Of the remaining trials, two compared combination-agent cisplatin with another chemotherapeutic regimen, three trials compared regimens of other platinum-containing agents, and three trials compared regimens of non-platinum-containing agents.

The methodological quality of the studies was deemed to be adequate for the purpose of deriving conclusions around the chemotherapeutic treatment of patients with recurrent, metastatic, or persistent cervical cancer. Changes in practice over time (i.e., the emergence of the use of radiosensitizers), the limited number of patients available to participate in the trials, and limitations in study design, such as a lack of blinding, contributed to this analysis of quality. Although three trials were stopped early, discontinuation was due to poor patient accrual and the termination of support. However, all of the trials were randomized, baseline characteristics were well balanced between treatment groups, and the

power to detect statistically significant differences between treatment groups was reported in a number of trials, as was the intention-to-treat principle.

See the original guideline document for a discussion of the evidence used to formulate the recommendations.

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

Report Approval Panel

Prior to the submission of this Evidence-Based Series report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. The Report Approval Panel reviewed the document and agreed that the report was well written and comprehensive. The Panel noted that the potential implications for the use of growth factors when using cisplatin and topotecan in combination should be discussed. In response to this comment, the use of growth factors was addressed in the Recommendations, Trial Characteristics, Discussion, and Conclusion sections. The Panel also indicated that the Discussion should contain a more sophisticated interpretation, specifically, how the methodological quality of the studies influenced the conclusions derived by the Gynecology Cancer Disease Site Group (DSG). In response, the methodological quality was summarized and contextualized in the Discussion section. The Panel also suggested minor editing and formatting revisions; these revisions were incorporated into the content.

External Review

Feedback was obtained through a mailed survey of 136 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. The survey was mailed out on May 23, 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gynecology Cancer DSG reviewed the results of the survey.

This report reflects the integration of feedback obtained through the external review process with final approval given by the Gynecology Cancer DSG and the Report Approval Panel of the Program in Evidence-based Care.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- It is recommended that all patients, particularly those who have been previously treated with cisplatin as a radiosensitizer, be offered the opportunity to participate in randomized trials, if available, that evaluate the efficacy and toxicity of other single-agent or combination chemotherapy regimens.
- Until further evidence becomes available, it is recommended that cisplatin in combination with topotecan should be offered to patients on the basis of improvements in response and survival outcomes when compared with single-agent cisplatin alone.
 - The improvement in outcomes must be weighed against significant increases in adverse events, especially hematological toxicities, and the degree of the clinical benefit. Despite the increase in toxicity, no significant differences in quality of life were detected. Severe hematological toxicities were managed by dose modification and the use of granulocyte-colony-stimulating factors (G-CSFs) in subsequent cycles.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- One trial reported statistically significant improvements in response rates (27% versus [vs.] 13%, $p=0.004$), progression-free survival (4.6 vs. 2.9 months, $p=0.014$), and median survival (9.4 vs. 6.5 months, $p=0.017$) in patients who received 50 mg/m² cisplatin on day 1 and 0.75 mg/m² topotecan on days 1 to 3, repeated every three weeks, when compared with patients treated with single-agent cisplatin.
 - In that trial, 57% of patients had been previously treated with cisplatin as a radiosensitizer.
 - As part of a subgroup analysis, median survival among patients not previously treated with cisplatin as a radiosensitizer was 15.4 months for patients treated with cisplatin and topotecan

versus 8.8 months among patients treated with cisplatin alone. In those previously treated with cisplatin as a radiosensitizer, median survival was 7.9 months versus 5.5 months, respectively (p-values not reported).

- In the remaining trials, where reported, the majority of patients did not receive chemotherapy as a radiosensitizer.
 - Three of these trials detected statistically significant improvements in overall response rates with cisplatin in combination with paclitaxel, BEM (bleomycin, vindesine, and mitomycin-C), or ifosfamide when compared with single-agent cisplatin.
 - Two trials reported a statistically significant progression-free survival advantage for patients receiving cisplatin in combination with paclitaxel or ifosfamide when compared with patients receiving single-agent cisplatin.
- Of the two trials that reported quality of life (QOL) data, no statistically significant differences were detected in patients treated with cisplatin in combination with topotecan or paclitaxel versus patients treated with single-agent cisplatin.

POTENTIAL HARMS

Significant increases in Grade 3 and 4 adverse events, especially severe hematological toxicities, were detected among patient treated with combination cisplatin-based chemotherapy when compared with patients who received cisplatin alone.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series 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 guarantees of any kind whatsoever regarding their content or use or application and disclaims any 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

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ADAPTATION

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

DATE RELEASED

2006 Jul 5

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 Gynecology 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 Gynecology Disease Site Group (DSG) were asked to disclose potential conflict of interest information. No conflicts were reported.

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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 for recurrent, metastatic, or persistent cervical cancer: a clinical practice guideline summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Jul 5. Various p. (Practice guideline; no. 4-20). 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 NGC summary was completed by ECRI on October 25, 2006. The information was verified by the guideline developer on November 24, 2006.

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