



## Complete Summary

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### GUIDELINE TITLE

First-line chemotherapy for postoperative patients with stage II, III or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

### BIBLIOGRAPHIC SOURCE(S)

Gynecology Disease Site Group. Covens A, Carey M, Bryson P, Verma S, Fung Kee Fung M. First-line chemotherapy for postoperative patients with stage II, III or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jan [online update]. 37 p. (Practice guideline report; no. 4-1-2). [64 references]

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## SCOPE

### DISEASE/CONDITION(S)

- Stage II, III, or IV epithelial ovarian cancer
- Fallopian tube cancer
- Primary peritoneal cancer

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness  
Treatment

### CLINICAL SPECIALTY

Obstetrics and Gynecology  
Oncology

### INTENDED USERS

Physicians

#### GUIDELINE OBJECTIVE(S)

To make recommendations regarding first-line chemotherapy for postoperative patients with stage II, III, or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer

#### TARGET POPULATION

- Women with newly diagnosed stage II, III (with or without measurable disease after surgery), or IV epithelial ovarian cancer who have not been previously treated with chemotherapy
- Women with fallopian tube and primary peritoneal cancers who have not been previously treated with chemotherapy

#### INTERVENTIONS AND PRACTICES CONSIDERED

First-line chemotherapy with the following regimens:

1. Intravenous (IV) carboplatin + paclitaxel (Taxol)
2. IV cisplatin + paclitaxel (Taxol)
3. IV carboplatin (single-agent)
4. Anthracyclines

Note: The incorporation of anthracyclines as part of first-line therapy is not recommended at the present time.

5. Intraperitoneal chemotherapy

Note: The use of intraperitoneal chemotherapy is not recommended at this time.

#### MAJOR OUTCOMES CONSIDERED

- Overall/median survival
- Treatment-related toxicity (e.g., Grade 3/4 nausea and vomiting; Grade 3/4 renal toxicity; Grade 3/4 neurotoxicity; Grade 3/4 neutropenia; Grade 3/4 thrombocytopenia; Grade 3/4 anemia; Grade 3/4 leukopenia)
- Quality of life

## 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: September 2001

The MEDLINE database was searched from 1980 to July 1999 using the strategy described in Appendix 1 of the original guideline document. The same search strategy was used to find additional citations in the CANCERLIT, CINAHL, and HealthStar databases. The Cochrane Library (Issue 2, 1999) was searched for additional randomized trials and systematic reviews. Proceedings of the 1999 meeting of the American Society of Clinical Oncology (ASCO), the 1999 meeting of the International Gynecologic Cancer Society (IGCS), and the 10th European Conference on Clinical Oncology, as well as reference lists of papers and review articles, were scanned for additional citations. The Physician Data Query (PDQ) clinical trials database [www.cancer.gov/search/clinical\\_trials/](http://www.cancer.gov/search/clinical_trials/) was searched for reports of ongoing randomized trials. The Canadian Medical Association Infobase [www.cma.ca/cpgs/index.asp](http://www.cma.ca/cpgs/index.asp), the National Guideline Clearinghouse [www.guideline.gov](http://www.guideline.gov) and other Web sites were searched for existing evidence-based practice guidelines. All searches were restricted to English-language publications. Update searches were conducted between January 2000 and April 2001 to find recently published evidence. In May 2000, the search was expanded to include randomized trials of chemotherapy for fallopian tube and primary peritoneal cancers.

## January 2004 Update

The original literature search has been updated using MEDLINE (April 2001 through January 2004), CANCERLIT (April 2001 through October 2002), the Cochrane Library (Issue 3, 2003), and the 2003 proceedings of the annual meeting of the American Society of Clinical Oncology.

## Inclusion Criteria

Articles were selected for inclusion in this practice guideline report if they met all of the following criteria:

1. They were reports of randomized controlled trials (RCTs) or meta-analyses of first-line chemotherapy for ovarian, fallopian tube, or primary peritoneal cancer. Comparisons of paclitaxel-and-platinum-based chemotherapy with platinum-based chemotherapy without paclitaxel, or comparisons of paclitaxel plus carboplatin with paclitaxel plus cisplatin as first-line treatment were of particular interest.
2. The trial included patients with stage II, III, or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (please see Appendix 2 of the original guideline document for staging information for ovarian cancer).
3. The article reported data on survival for each intervention group.

Clinical trial results reported in either full papers or abstracts were eligible. Evidence-based clinical practice guidelines from other guideline-development groups were also eligible for inclusion.

## Exclusion Criteria

1. Studies that evaluated the use of chemotherapy with bone marrow or stem cell transplantation were excluded.
2. Because resources available for translation were limited, foreign language publications were excluded.

#### NUMBER OF SOURCE DOCUMENTS

Original Guideline: September 2001

Survivor benefits: 2 meta-analyses and 7 randomized controlled trials (RCTs)  
Potential harms: 13 RCTs

January 2004 Update

One of the randomized controlled trials that was presented in abstract form in the original guideline document has been published in a full report. In addition, abstracts of five RCTs have been identified as well as two full publications of RCTs.

#### 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

Meta-Analysis  
Review of Published Meta-Analyses  
Systematic Review with Evidence Tables

#### DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Original Guideline: September 2001

The intention was to pool mortality data from randomized trials of first-line treatments for ovarian cancer, where there were common treatment and control groups and where published meta-analyses were not available.

Data on grade 3 and 4 adverse effects from studies with similar experimental and control groups were pooled using Metaanalyst<sup>0.988</sup> software provided by Dr. Joseph Lau (Boston, MA). Results are expressed as risk ratios (RR) with 95% confidence intervals (CI). The random effects model was used as the more conservative estimate of effect.

January 2004 Update

The information above remains intact.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

### DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Original Guideline: September 2001

After reviewing the first draft of the guideline report, there was consensus among the Disease Site Group (DSG) members that randomized trials have demonstrated a survival advantage for paclitaxel plus platinum as first-line treatment for ovarian cancer. Other issues addressed in discussion of the guideline included single-agent versus combination chemotherapy, carboplatin versus cisplatin, the preferred doses for paclitaxel, carboplatin and cisplatin, the appropriate duration of the paclitaxel infusion, the number of cycles of treatment, the addition of anthracyclines to first-line treatment, and the role of intraperitoneal therapy. For some of these issues, only indirect evidence from trials conducted before the introduction of paclitaxel is available, and direct evidence from trials with paclitaxel is emerging. The DSG suggested that more detailed descriptions of data on adverse effects and quality of life from randomized controlled trials (RCTs) should be added to the guideline report for the next draft. Recommendations suggested by the DSG members at the meeting where the first draft was discussed included:

- Carboplatin plus paclitaxel should be the standard treatment for stage II-IV ovarian cancer.
- Carboplatin may be given in doses ranging from area under the curve (AUC) of 5-6.
- Paclitaxel may be used in doses ranging from 135 to 175 mg/m<sup>2</sup> given over 3 to 24 hours.
- Intraperitoneal cisplatin plus intravenous paclitaxel is a reasonable treatment option for patients with stage III optimal disease.
- The use of carboplatin as a single agent seems a reasonable alternative for women in whom one wants to minimize toxicity. This is particularly relevant for elderly and medically infirm patients.

The DSG decided to expand the target population for the guideline to include women with fallopian tube and primary peritoneal cancers.

During the subsequent development of the guideline report, the DSG refined several of their original conclusions and recommendations.

- They considered the rationale for recommending carboplatin over cisplatin. While there is no convincing evidence of the superiority of carboplatin over cisplatin in terms of survival, in the opinion of the DSG, the hematologic toxicity imposed by carboplatin is qualitatively preferable to the gastrointestinal and neurologic toxicity imposed by cisplatin.
- Although the evidence is indirect, randomized trials comparing paclitaxel administered at a dose of 175 mg/m<sup>2</sup> over three hours with a dose of 135 mg/m<sup>2</sup> over 24 hours did not detect a survival difference between these two regimens. It has therefore become common practice to use a three-hour

infusion of paclitaxel due to its convenience. The Disease Site Group recommends that paclitaxel be administered as a three-hour infusion at a dose of either 135 to 175 mg/m<sup>2</sup>.

- No recommendation was made about intraperitoneal chemotherapy. Given the fact that only one study has demonstrated a statistically significant survival benefit for intraperitoneal chemotherapy, it is difficult to consider it as standard therapy or to recommend its use at this time.
- Because of the limited evidence available, the DSG did not include the use of anthracyclines in first-line therapy in the recommendations. As the addition of doxorubicin increases toxicity, and the magnitude of the survival benefit is unclear, the DSG does not recommend the incorporation of anthracyclines as part of first line therapy at the present time. It is hoped that this issue will be clarified by several of the ongoing trials listed in the original guideline document.
- Although there are no randomized trials of chemotherapy in fallopian tube cancer or primary peritoneal cancer, given that most clinicians treat women with these uncommon cancers as they would patients with ovarian cancer, the DSG felt that the recommendations for ovarian cancer could be applied to fallopian tube and primary peritoneal cancer.

A revised draft of the practice-guideline report was reviewed by the DSG in November 2000 and approved for distribution to practitioners in Ontario for their feedback. In April 2001, following the practitioner feedback survey, the DSG reviewed the status of the International Collaborative Ovarian Neoplasm Study (ICON3) trial. Full results of this RCT, which will provide evidence on carboplatin alone versus carboplatin plus paclitaxel, have yet to be published. The ICON3 study was conducted in Europe using a different staging system and with general surgeons performing surgery for ovarian cancer. When the study results are published, the DSG will review them, assess their generalizability to the Ontario setting and update the guideline report.

#### January 2004 Update

In November 2002, the Gynecology DSG met to discuss the results of the ICON3 trial. The DSG decided to modify the recommendation of carboplatin plus paclitaxel to carboplatin with or without paclitaxel because the results of the ICON3 trial detected that there was no difference in survival between the three treatment groups: paclitaxel plus carboplatin; carboplatin alone; and cyclophosphamide, doxorubicin, and cisplatin.

#### 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 54 practitioners in Ontario (41 medical oncologists and 13 gynecologic oncologists). 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 two weeks (post card) and four weeks (complete package mailed again). The Gynecology Disease Site Group reviewed the survey results. Thirty-six completed surveys were returned (66%).

Following practitioner feedback, the practice guideline was reviewed by the Practice Guidelines Coordinating Committee. In response to feedback from the Coordinating Committee, the Gynecology Disease Site Group added qualifying statements on the use of anthracyclines and intraperitoneal therapy in first-line chemotherapy for ovarian cancer. Minor changes were made to the summary, full report, and the format of the recommendations in the interest of clarity. Final approval of the practice guideline report was obtained from the Practice Guidelines Coordinating Committee.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

- Intravenous carboplatin with or without paclitaxel is the recommended postoperative chemotherapy regimen for newly diagnosed stage II-IV epithelial ovarian cancer.
- Intravenous cisplatin plus paclitaxel may also be considered as a treatment option.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Original Guideline: September 2001

Two individual-patient-data meta-analyses and seven additional randomized trials investigated the survival benefits associated with various options for first-line

systemic chemotherapy for advanced ovarian cancer. One additional randomized trial, reported only in abstract form, evaluated quality of life.

Data on the adverse effects of platinum-based chemotherapy in this setting were available from 13 randomized trials.

January 2004 Update

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

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Original Guideline: September 2001

- Compared with non-platinum-based regimens, platinum, alone or in combination with other agents, improves survival when used as first-line treatment for ovarian cancer (mortality hazard ratio, 0.88; 95% confidence interval, 0.79 to 0.98, n=1,704).
- A meta-analysis involving 2,219 patients detected no difference in efficacy between cisplatin and carboplatin (hazard ratio for death, 1.02; 95% confidence interval, 0.93 to 1.12).
- A published randomized trial of cisplatin plus paclitaxel (n=108) versus carboplatin plus paclitaxel (n=100) detected no significant difference in survival between these regimens (hazard ratio for death, 0.85; 95% confidence interval, 0.59 to 1.24).
- In two randomized trials, treatment with paclitaxel plus cisplatin resulted in improved survival compared with cyclophosphamide plus cisplatin (relative risk, 0.6; 95% confidence interval, 0.5 to 0.8 for one study; and hazard ratio, 0.7; 95% confidence interval, 0.6 to 0.9 for the other).
- A randomized trial of paclitaxel plus cisplatin versus paclitaxel alone versus cisplatin alone detected no differences in survival among the three treatment groups.

January 2004 Update

A randomized trial of paclitaxel plus carboplatin versus carboplatin alone versus cyclophosphamide, doxorubicin, and cisplatin detected no differences in survival amongst the three groups.

### POTENTIAL HARMS

Original Guideline: September 2001

- While hematologic adverse effects are more frequent with carboplatin than with cisplatin (relative risk for grade 3/4 thrombocytopenia, 0.19; 95% confidence interval, 0.14 to 0.25; where a relative risk <1 favours cisplatin), non-hematologic adverse effects are less frequent with carboplatin (relative risk for grade 3/4 nausea & vomiting, 1.63; 95% confidence interval, 1.28 to

2.07; relative risk for neurotoxicity, 2.40; 95% confidence interval, 1.67 to 3.45; where a relative risk >1 favours carboplatin).

- The addition of paclitaxel to cisplatin does not appear to increase the incidence of serious adverse effects. Data on the toxicity of paclitaxel plus carboplatin are not available from randomized trials.

January 2004 Update

- Paclitaxel plus carboplatin appears to increase the incidence of sensory neuropathy, when compared to carboplatin alone or cyclophosphamide, doxorubicin, and cisplatin.
- There is less nausea associated with paclitaxel plus carboplatin than cyclophosphamide, doxorubicin, and cisplatin.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- Because the addition of doxorubicin to chemotherapy increases toxicity and the magnitude of the survival benefit is unclear, the incorporation of anthracyclines as part of first-line therapy is not recommended at the present time.
- Given that only one study has demonstrated a statistically significant survival benefit for intraperitoneal chemotherapy, its use is not recommended at this time.
- The recommendation that carboplatin be used without paclitaxel is based on the results of one large randomized study (International Collaborative Ovarian Neoplasm Study [ICON3]). There are some important differences between the ICON3 trial and the other randomized controlled trials.
- Although there are no randomized trials of chemotherapy in fallopian tube cancer or primary peritoneal cancer, given that most clinicians would treat women with these uncommon cancers as they would patients with ovarian cancer, the authors of this guideline feel the recommendations made above can be applied to fallopian tube and primary peritoneal cancers.
- 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)

Gynecology Disease Site Group. Covens A, Carey M, Bryson P, Verma S, Fung Kee Fung M. First-line chemotherapy for postoperative patients with stage II, III or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jan [online update]. 37 p. (Practice guideline report; no. 4-1-2). [64 references]

### ADAPTATION

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

### DATE RELEASED

2001 Sep 21 (revised online 2004 Jan)

### 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 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 disclosed potential conflict of interest information.

#### GUIDELINE STATUS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

#### 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:

- First-line chemotherapy for postoperative patients with stage II, III or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. Summary. Toronto (ON): Cancer Care Ontario. 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 Feb; 13(2): 502-12.
- Covens A, Carey M, Bryson P, Verma S, Fung Kee Fung M, Johnston M. Systematic review of first-line chemotherapy for newly diagnosed postoperative patients with stage II, III, or IV epithelial ovarian cancer. *Gynecol Oncol* 2002 Apr; 85(1): 71-80.

#### PATIENT RESOURCES

None available

#### NGC STATUS

This NGC summary was completed by ECRI on May 13, 2004. The information was verified by the guideline developer on June 2, 2004.

#### COPYRIGHT STATEMENT

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