Complete Summary

GUIDELINE TITLE

The role of intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Elit L, Oliver T, Covens A, Kwon J, Fung-Kee-Fung M, Hirte H, Oza A, Gynecology Cancer Disease Site Group. The role of intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Aug 3. 23 p. (Evidence-based series; no. 4-21). [26 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.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Stage III epithelial ovarian cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Obstetrics and Gynecology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the role of intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer

TARGET POPULATION

Women with stage III epithelial ovarian cancer for whom first-line chemotherapy after cytoreductive surgery is being considered

INTERVENTIONS AND PRACTICES CONSIDERED

Intraperitoneal chemotherapy with a platinum agent and a taxane (e.g., cisplatin/paclitaxel)

MAJOR OUTCOMES CONSIDERED

- Response
- Survival
- Toxicity
- Catheter-related complications
- 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

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

The literature was searched using MEDLINE (OVID: 1966 through January 2006), EMBASE OVID: (1988 through January 2006), the Cochrane Library (OVID; Issue 4, 2005), the Physician Data Query database, the Canadian Medical Association

Infobase, and the National Guideline Clearinghouse. In addition, the abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (1997-2005) and the European Society for Medical Oncology (2002, 2004) were searched for evidence relevant to this report. Reference lists of related papers and recent review articles were also scanned for additional citations.

The literature search of the electronic databases combined disease specific terms (ovarian neoplasms/ or ovar:.ti and cancer.ti. or neoplasms/) with treatment specific terms (intraperitoneal.ti. or ip.ti or peritoneal.ti.) for the following study designs: randomized controlled trials, practice guidelines, systematic reviews, and meta-analyses.

Study Selection Criteria

Articles were to be selected for inclusion in the systematic review of the evidence if they were published reports or published abstracts of randomized trials that compared patients with advanced (stage III) epithelial ovarian cancer to first-line treatment involving intraperitoneal-containing chemotherapy versus first-line treatment involving intravenous chemotherapy only. Trials were to report data on some or all of the outcomes of interest: response, survival, toxicity, catheter-related complications, and/or quality of life.

Practice guidelines, meta-analyses, or systematic reviews explicitly based on randomized trials related to the guideline question were also considered eligible for inclusion in the systematic review.

Articles were excluded if treatment included immunotherapy, intraperitoneal radioactive phosphorus (^{32}P), or hyperthermia. Trials were also excluded if they were reported in a language other than English, and data could not be extracted.

NUMBER OF SOURCE DOCUMENTS

Seven randomized controlled trials and one systematic review with meta-analyses met the inclusion criteria and were deemed eligible for inclusion in the systematic review of the evidence. An additional paper, reporting further information on the Gynecology Oncology Group (GOG) 172 trial was also identified, and data on catheter-related outcomes were extracted from that paper.

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 of Randomized Controlled Trials
Review of Published Meta-Analyses
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. Where appropriate, data on outcomes of interest are pooled across trials, using Hazards Ratios (HR), or with the Relative Risk (RR) using clinically relevant events or time-points. Data were pooled using Review Manager 4.0.3 (Metaview© Update Software), obtained through the Cochrane Collaboration (www.cochrane.org). Results are expressed as the HR or RR with 95% confidence intervals (CI), where an RR less than 1.0 favours the experimental treatment and an RR greater than 1.0 favours control. The random effects model is generally preferred over the fixed effects model as the more conservative estimate of effect. The number of patients needed to treat for one additional patient to benefit (NNT) is calculated using the inverse of the risk difference. Where appropriate, sensitivity analyses are conducted to determine whether particular study characteristics influence the estimate of effect.

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 the role of intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

The results from the seven randomized trials identified have shown that deriving conclusions regarding the role of intraperitoneal chemotherapy in treating women with epithelial ovarian cancer is complex. While not ideal, the methodological quality of the randomized trials was deemed to be adequate for the purpose of deriving conclusions around the role of intraperitoneal chemotherapy. Of the three larger and four smaller trials, the baseline patient characteristics were reported to be well-balanced between treatment groups, completeness of follow-up was greater than 80%, the power and patient accrual to detect statistically significant differences between treatment groups was sufficient in the three larger trials, the intention-to-treat principle was employed in five trials, and there were data from six of the trials sufficient for pooling a clinically relevant outcome measure, overall survival. Overall, to derive conclusions based upon the evidence, the emphasis was placed largely on the results of the three larger trials that, in spite of differences in trial designs and treatment regimens, were adequately powered to detect statistically significant differences between treatment groups. It was also important to consider the results of the entire body of evidence in the context of

the historical development of intraperitoneal chemotherapy tested in the randomized setting to date.

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 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 gave formal approval of the document as written but did provide minor suggestions to consider. Aside from minor editorial and formatting comments, the Report Approval Panel suggested that it would be worthwhile to include a discussion of how the factors related to trial quality and characteristics influenced the conclusions derived from the Disease Site Group (DSG). The Panel also suggested that overall survival, which was included in the text, be added to the tables to help inform the reader, and a comment on the methodological aspects pertaining to the meta-analysis be added to the Discussion. In response, a section on the methodological assessment of the trials was added to the Discussion, five-year progression free and overall survival were added to the tables, and it was reported that, while presented, five-year progression-free and overall survival data were not study endpoints but were used mainly to pool results across trials. Finally, given the subtle shift in survival presentation, a comment was added to the Discussion on the information that comprised the evidentiary basis of this series, of which the meta-analysis was part.

External Review

Practitioner feedback was obtained through a mailed survey of 221 practitioners in Ontario (radiation oncologists, surgeons, medical oncologists, gynecologists, and general practitioners). 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 practitioner feedback survey was mailed out on April 28, 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again).

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

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- As front-line therapy, the intravenous administration of a platinum agent and a taxane remains a standard of care for this patient population. Cisplatin-containing intraperitoneal chemotherapy should be offered to patients on the basis of significant improvements in progression-free and overall survival when compared with cisplatin-containing intravenous chemotherapy alone.
    - The survival benefits associated with intraperitoneal chemotherapy must be weighed against the statistically significant increases in toxicity and catheter-related complications.
        - For patients with residual tumour diameter $\leq$1 cm in any one area, significant survival benefits were detected with intraperitoneal chemotherapy.
        - For patients with disease volumes >1 cm in any one area, the role of intraperitoneal chemotherapy is yet to be defined.
    - The optimal intraperitoneal chemotherapy regimen has yet to be defined. The greatest median survival benefits were detected with intraperitoneal cisplatin and paclitaxel; however, only 42% of patients were able to complete all six cycles of the assigned treatment.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

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

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Seven randomized trials form the evidence basis for this report. All seven trials investigated the role of intraperitoneal chemotherapy in the front-line treatment of patients with stage II to IV ovarian cancer.

- Three trials detected statistically significant overall survival benefits with intraperitoneal-containing chemotherapy when compared with intravenous chemotherapy alone.
    - In the three trials, the survival benefits associated with intraperitoneal cisplatin-containing chemotherapy were eight, 11, and 16 months longer than the survival rates observed with intravenous chemotherapy alone. The greatest median survival benefits were detected in patients randomized to receive 135 mg/m^2 of intravenous paclitaxel on day 1 over 24 hours, 100 mg/m^2 of intraperitoneal cisplatin on day 2, and 60 mg/m^2 of intraperitoneal paclitaxel on day 8, repeated every 21 days for six cycles.
    - The remaining four trials were underpowered to detect significant differences between treatment groups.
- With a relative risk of 0.88 (95% confidence interval [CI], 0.81-0.95; number needed to treat [NNT] = 12.5) for overall survival, the pooled data confirms that treatment involving intraperitoneal chemotherapy extends overall survival when compared with intravenous chemotherapy alone.

POTENTIAL HARMS

- Across six trials that reported data, 24 to 75% of patients were unable to complete all of the assigned cycles of the intraperitoneal chemotherapy regimen.
    - Severe adverse events with intraperitoneal chemotherapy were significantly more common when compared with intravenous chemotherapy alone and were often dose limiting.
    - Catheter-related complications included abdominal pain, bleeding, infection, peritonitis, catheter blockage, leakage, movement, malfunction, and/or access problems.
- One trial reported significantly poorer quality of life for patients treated with intraperitoneal chemotherapy when assessed prior to randomization, before the fourth cycle, and at three to six weeks after the sixth cycle. The difference in quality of life scores was not significant at 12 months after the completion of the sixth cycle of chemotherapy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

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)

Elit L, Oliver T, Covens A, Kwon J, Fung-Kee-Fung M, Hirte H, Oza A, Gynecology Cancer Disease Site Group. The role of intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Aug 3. 23 p. (Evidence-based series; no. 4-21). [26 references]

ADAPTATION

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

DATE RELEASED

2006 Aug 3

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

None declared

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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:

- The role of intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a clinical practice guideline summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Aug 3. Various p. (Practice guideline; no. 4-21). 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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