Evidence-based Series 4-1-2 EDUCATION AND INFORMATION-2013

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

First-line Chemotherapy for Postoperative Patients with Stage II, III or IV Epithelial Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer

Members of the Gynecology Cancer Disease Site Group

Evidence-based Series 4-1-2 was reviewed in 2012 and put in the Education and Information section by the Gynecology Cancer Disease Site Group (DSG) on November 29, 2012. See Section 3: Document Review Summary and Tool for details. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

The reviewed EBS report, consists of

Section 1: Clinical Practice Guideline (EDUCATION AND INFORMATION)
Section 2: Systematic Review
Section 3: Document Review Summary and Tool
and is available on the CCO Web site (http://www.cancercare.on.ca)
PEBC Gynecologic Cancer Disease Site Group page at:
https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/gynecologic_cancer/

Release Date: July 25, 2013

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
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Guideline Report History

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Evidence-based Series # 4-1-2 (ARCHIVED 2013): Section 1

First-line Chemotherapy for Postoperative Patients with Stage II, III or IV Epithelial Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer

A. Covens, M. Carey, P. Bryson, S. Verma, M. Fung Kee Fung, and members of the Gynecology Disease Site Group

ORIGINAL GUIDELINE: September 21, 2001
MOST RECENT LITERATURE SEARCH: June 2004
NEW EVIDENCE ADDED TO GUIDELINE REPORT: June 2004
RECOMMENDATIONS MODIFIED: June 2004

Based on new evidence that has emerged since completion of the original guideline, the Gynecology Cancer Disease Site Group has modified this practice guideline report. The revised recommendations and supporting evidence are labelled Update.

SUMMARY

Stage II-IV Ovarian Cancer
Guideline Question
What is the optimal postoperative chemotherapy regimen for women with stage II, III (micro or macro) or IV epithelial ovarian cancer who are newly diagnosed and who have not previously received chemotherapy?

Target Population
These recommendations apply to postoperative patients 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.

Recommendations
Update
- Intravenous carboplatin with or without paclitaxel or docetaxel is the recommended postoperative chemotherapy regimen for newly diagnosed stage II-IV epithelial ovarian cancer.
  - Paclitaxel in combination with carboplatin is associated with greater neurotoxicity than docetaxel and carboplatin, however, the combination of docetaxel and carboplatin is associated with more myelosuppression than paclitaxel and carboplatin. The differences in the toxicity profiles should be discussed with patients when choosing the most appropriate regimen.
• Intravenous cisplatin plus paclitaxel may also be considered as a treatment option.

**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.

• At least one study has demonstrated a statistically significant survival benefit associated with intraperitoneal chemotherapy, although this finding is not consistent across all such trials. When the potential morbidity associated with intraperitoneal chemotherapy is considered, the overall benefit is likely to be small. Therefore, its use is not recommended at this time.

• The recommendation that carboplatin can be used without paclitaxel is based on the results of one large randomized study (ICON3). There are some important differences between the ICON3 trial and the other RCTs (outlined in the Interpretive Summary).

• The recommendation that either paclitaxel or docetaxel is acceptable to be used in combination with carboplatin is based on the results of a randomized trial that compared docetaxel and carboplatin to paclitaxel and carboplatin. Survival data indicate that there is not a significant difference in progression-free and overall survival between the two treatment groups. There was significantly more myelosuppression reported in the docetaxel and carboplatin arm compared to the paclitaxel and carboplatin arm, and there was significantly more neurotoxicity reported in the paclitaxel and carboplatin arm than the docetaxel and carboplatin arm.

**Dose and Schedule of Administration**

Although no randomized trials have compared different doses of cisplatin, carboplatin or paclitaxel in combination in first-line therapy for ovarian cancer, experience gained from the use of these agents in randomized trials suggests that the following doses are reasonable: 135 to 175 mg/m^2^ of paclitaxel over three hours and carboplatin at area under the curve 5 to 6 or cisplatin at 75 mg/m^2^.

**Fallopian Tube Cancer and Primary Peritoneal Cancer**

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 authors of this guideline feel the recommendations made above can be applied to fallopian tube and primary peritoneal cancers.

**Methods**

A systematic search of the MEDLINE, EMBASE, CANCERLIT, HealthStar, CINAHL®, Cochrane Library, and Physician Data Query Clinical Trials databases was performed for the period from 1980 to June 2004. Reference lists and meeting abstracts were scanned for additional citations. Randomized controlled trials or meta-analyses of first-line chemotherapy in patients with stage II, III or IV epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer were eligible for inclusion in this review of the evidence. Survival, quality of life, and adverse effects were the outcomes of interest.

Evidence was selected and reviewed by four members of the Practice Guidelines Initiative’s Gynecology Disease Site Group. This practice guideline report has been reviewed and approved by the Gynecology Disease Site Group, comprised gynecologic oncologists, medical oncologists, radiation oncologists, an oncology nurse, a pathologist, a patient representative, and methodologists.
External review by Ontario practitioners is obtained for all practice guidelines through a mailed survey. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and integration of relevant new literature into the guideline report.

Key Evidence

**Benefits**

- 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 of these randomized trials, reported only in abstract form, evaluated quality of life.
- 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=1704).
- A meta-analysis involving 2219 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 0.9 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.

**Update**

- A randomized trial of paclitaxel plus carboplatin versus carboplatin alone versus cyclophosphamide, doxorubicin, and cisplatin detected no differences in survival among the three groups.
- A randomized trial comparing paclitaxel and carboplatin to docetaxel and carboplatin detected no significant differences in progression-free or two-year survival between the treatment arms.
- Two randomized trials comparing paclitaxel and carboplatin to paclitaxel, carboplatin, and epirubicin detected no significant differences in response rate, progression-free survival or overall survival between the treatment arms. One study reported that the addition of epirubicin to the regimen substantially increased toxicity.

**Harms**

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

**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.
- A randomized trial comparing paclitaxel and carboplatin to docetaxel and carboplatin reported more neurotoxicity and less myelosuppression in the women receiving paclitaxel and carboplatin compared to the women receiving docetaxel and carboplatin.

**Related Guidelines**
Practice Guidelines Initiative Evidence Summary Report #4-3: *Chemotherapy for Recurrent Epithelial Ovarian Cancer Previously Treated with Platinum.*

For further information about this practice guideline, please contact:
Dr. Michael Fung Kee Fung, Chair, Gynecology Disease Site Group; Ottawa General Hospital, 501 Smyth Road, Ottawa, Ontario; Telephone: 613-737-8560, FAX: 613-737-8828.

The Practice Guidelines Initiative is sponsored by: Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

Visit http://www.cancercare.on.ca/access_PEBC.htm for all additional Practice Guidelines Initiative reports.
PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.1 The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:
First-line Chemotherapy for Postoperative Patients with Stage II, III or IV Epithelial Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer

Members of the Gynecology Disease Site Group

FULL REPORT

I. QUESTIONS
What is the optimal postoperative chemotherapy regimen for women with stage II, III (micro or macro) or IV epithelial ovarian cancer who are newly diagnosed and who have not previously received chemotherapy? What is the optimal postoperative chemotherapy regimen for women with fallopian tube or primary peritoneal cancers, who are newly diagnosed and who have not previously received chemotherapy?

II. CHOICE OF TOPIC AND RATIONALE
The past 25 years have seen significant advances in the chemotherapy used to treat ovarian cancer that has spread beyond the ovary. While the use of adjuvant chemotherapy in stage I disease is controversial, no such debate exists for stages II-IV. In the mid 1970's, cisplatin became recognized as a significant drug in the treatment of ovarian cancer, and through randomized studies, was adopted as part of first-line chemotherapy regimens. Since then, numerous issues have arisen: the question of single-agent platinum versus multi-agent chemotherapy, the choice of platinum agents (given the development of carboplatin), and finally, the demonstration of superior survival results with the use of paclitaxel (Taxol) in combination with a platinum analogue. The histology and embryology, and the patterns of spread (i.e., the natural history), of these cancers are similar to those of ovarian cancer. Therefore, most clinicians treat women with fallopian tube and primary peritoneal cancers as they would patients with ovarian cancer.

The Gynecology Disease Site Group (DSG) determined that an evidence-based practice guideline on first-line chemotherapy would be useful to practitioners in Ontario. The guideline report would provide a vehicle for describing and interpreting recently published new evidence on the use of platinum and paclitaxel in stage II-IV ovarian cancer, and for addressing the issues around cisplatin versus carboplatin. At present, standard first-line chemotherapy for ovarian cancer in Ontario consists of paclitaxel plus carboplatin, but there is variation from centre to centre in terms of dose, duration of the paclitaxel infusion, and the number of cycles of treatment given.

III. METHODS
Guideline Development
This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario’s Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (1). Evidence was selected and reviewed by four members of the PGI’s Gynecology Disease Site Group. The summary of the evidence was then reviewed by...
the full Gynecology DSG, which is comprised of gynecologic oncologists, medical oncologists, radiation oncologists, an oncology nurse, a pathologist, a patient representative, and methodologists. Members of the Gynecology DSG disclosed potential conflict of interest information.

The clinical practice guideline report is a convenient and up-to-date source of the best evidence on first-line chemotherapy for epithelial ovarian cancer, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario, and the Ontario Ministry of Health and Long-term Care.

External review by Ontario practitioners is obtained for all practice guideline reports through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and integration of relevant new literature into the guideline report.

**Literature Search Strategy**

The MEDLINE database was searched from 1980 to July 1999 using the strategy described in Appendix 1. 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 on the Internet (http://cnetdb.nci.nih.gov/trialsrch.shtml) was searched for reports of ongoing randomized trials. The Canadian Medical Association Infobase (http://www.cma.ca/cpgs/index.asp), the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp), and other web sites were searched for existing evidence-based practice guidelines. All searches were restricted to English-language publications.

**Update**

The original literature search has been updated using MEDLINE (through June 2004), EMBASE (through week 25 2004), CANCERLIT (through October 2002), the Cochrane Library (Issue 2, 2004), and the 2000 to 2004 proceedings of the annual meeting of the American Society of Clinical Oncology. In May 2000, the search was expanded to include randomized trials of chemotherapy for fallopian tube and primary peritoneal cancers.

**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 (RCT) 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 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.

Synthesizing the Evidence
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. Please see page 9 for further details.

Data on grade 3 and 4 adverse effects from studies with similar experimental and control groups were pooled using Metaanalyst 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 (2).

IV. RESULTS
Literature Search Results
Practice Guidelines
No completed evidence-based clinical practice guidelines on first-line chemotherapy were found by the original literature search. Two interim recommendations on the use of paclitaxel as first-line chemotherapy were available in December 1999; one was prepared by an Interim Policy Recommendations Working Group for Cancer Care Ontario in March 1998 (unpublished), and the second was prepared by the National Health Service-sponsored Development and Evaluation Service for a regional health authority in the United Kingdom in June 1996 (http://www.hta.nhsweb.nhs.uk/rapidhta/publications.htm). New evidence from randomized trials has become available since these interim reports were completed.

A British practice guideline from the National Institute for Clinical Excellence (NICE) was published on their Web site in May 2000 (http://www.nice.org.uk/nice-web/Embcat.asp?page=oldsite/appraisais/tax_guide.htm), after the first draft of the PGI guideline had been completed. The NICE guideline has replaced the interim recommendations drafted by the Development and Evaluation Service in 1996. The NICE guideline was based on a systematic review of the effectiveness of the taxanes in the treatment of advanced breast and ovarian cancer (http://www.nice.org.uk/nice-web/pdf/hta_ov_taxanes.pdf), which reviewed data from the GOG-11 (3), GOG-132 (4), Intergroup OV10 (5), and ICON3 (6) randomized trials of first-line treatment for ovarian cancer. (The most recently published results from these RCTs are reviewed below). The guideline developers recommended “paclitaxel in combination with platinum therapy (cisplatin or carboplatin)” as “standard initial therapy for patients with ovarian cancer following surgery”.

Published Meta-analyses
Two meta-analyses, based on individual patient data, were eligible for inclusion in this review of the evidence (7-9). In a series of meta-analyses published in 1998, the Advanced Ovarian Cancer Trialists’ Group pooled individual-patient data from randomized trials of platinum-containing versus non-platinum chemotherapy, combination versus single-agent chemotherapy, and cisplatin versus carboplatin (7). This review was also posted in the Cochrane Library in September 1998 (8). In 1991, the Ovarian Cancer Meta-analysis Project pooled individual-patient data from four randomized trials comparing cyclophosphamide plus cisplatin with cyclophosphamide/doxorubicin/cisplatin (9).
**Randomized Controlled Trials**

Table 1 lists the evidence available for this practice guideline. The majority of the patients enrolled in the RCTs were women with ovarian cancer. The GOG trials included a small number of patients with fallopian tube and primary peritoneal cancers, but no randomized trials restricted to these cancers were found.

In addition to the RCTs included in the meta-analyses described above, survival data were available from ten recent randomized trials (3,10-18). Eight of these addressed questions not covered in the trials of first-line treatment included in the meta-analyses: four examined the role of paclitaxel (3,10-12), three studied the use of intraperitoneal platinum (13,14,15), and two compared cisplatin and carboplatin, administered with paclitaxel (16,18). The ninth RCT compared single-agent carboplatin with a multi-agent cisplatin-based regimen (17).

Data on adverse effects were available from ten trials of carboplatin versus cisplatin (18-27,29)—including three trials where paclitaxel was administered in both treatment arms (18,25,26,29)—from three trials of platinum plus paclitaxel versus platinum-based regimens without paclitaxel (3,11,12), and from one trial of epirubicin (28).

Quality of life was assessed in only one RCT of first-line chemotherapy, a trial of carboplatin plus paclitaxel versus cisplatin plus paclitaxel (25,29).

Six randomized trials and one pooled analysis examined the relationship of dose, schedule and duration of treatment with survival (30-36).

**Update**

The ICON3 trial, one of the RCTs that examined the role of paclitaxel, was presented in abstract form in the original practice guideline (10). Since the publication of the original practice guideline the ICON3 has been published in a full report (1u). The full report provides toxicity details in addition to detailed survival analyses comparing three treatment arms: paclitaxel plus carboplatin; carboplatin alone; and cyclophosphamide, doxorubicin and cisplatin (CAP).

Since the publication of the ICON3 trial, five abstracts of RCTs have been identified that compare first-line chemotherapy regimens in women with advanced ovarian cancer (2u-6u). At this time, the results of all five RCTs are preliminary and there are no survival data available. The Gynecology DSG will periodically scan the literature for the full publications of these RCTs and update this practice guideline as the RCTs are published.

Two full publications of RCTs are also currently available (7u-8u). Both RCTs compared paclitaxel with cisplatin or paclitaxel with carboplatin in women with advanced ovarian cancer.

Three abstracts of new RCTs (9u-11u) have been published since the original guideline was completed. One of the abstracts compared paclitaxel and carboplatin to docetaxel and carboplatin in women with advanced ovarian cancer (9u). The other two abstracts randomized women with advanced ovarian cancer to receive paclitaxel and carboplatin with or without epirubicin (10u,11u).
Table 1. Summary of the evidence used to inform the PGI practice guideline on first-line chemotherapy for postoperative patients with stage II, III or IV epithelial ovarian cancer.

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Note: vs., versus.
Abstract reports of two additional RCTs were found during an update search in May 2000: a trial of alternating carboplatin and cisplatin plus paclitaxel versus carboplatin plus paclitaxel (37), and a trial of oxaliplatin plus cyclophosphamide versus cisplatin plus cyclophosphamide (38). These were not directly relevant to the key issues of the addition of paclitaxel to platinum-based chemotherapy and carboplatin versus cisplatin and are not discussed further.

A list of acronyms for the trials described in this practice guideline report appears in Appendix 3.

**Clinical Outcomes**

**Survival**

**Platinum**

Randomized trials have demonstrated that platinum, alone or in combination with other agents, improves survival compared to non-platinum-based chemotherapy when used as first-line treatment for ovarian cancer. Data from nine RCTs of platinum-based chemotherapy versus non-platinum-based chemotherapy were pooled by the Advanced Ovarian Cancer Trialists’ Group (7). This individual-patient-data meta-analysis detected a survival benefit when platinum was used for chemotherapy (Mortality hazard ratio [HR], 0.88; 95% CI, 0.79 to 0.98; p=0.02; n=1704). This translates into an absolute improvement of approximately 5% in the survival rate at two years (35% without platinum versus 40% with platinum).

**Platinum plus Paclitaxel**

Three completed, fully published randomized trials of cisplatin plus paclitaxel versus cisplatin without paclitaxel (3,11,12) and one ongoing trial reported in an abstract (10) are described in Table 2. In two randomized trials, treatment with paclitaxel plus cisplatin resulted in improved survival compared with cyclophosphamide plus cisplatin (3,12). A randomized trial of paclitaxel plus cisplatin versus paclitaxel alone versus cisplatin alone detected no differences in survival among the three treatment groups (11). Only preliminary results are available for the fourth trial (10).

GOG-111 detected a significant survival advantage for patients treated with six cycles of cisplatin/paclitaxel over patients treated with cisplatin/cyclophosphamide (3). A similar Intergroup randomized trial in a more heterogeneous group of patients (including stages II and optimal III) also detected a significant survival advantage for the paclitaxel-containing regimen (12). Forty-eight percent of the women in the cisplatin/cyclophosphamide arm were crossed over to paclitaxel at progression of disease. Participants with stable or responding disease after six cycles of treatment in the Intergroup trial had the option of receiving three additional cycles. Twenty-six percent of the cyclophosphamide/cisplatin group and 33% of the paclitaxel/cisplatin group received more than six cycles of chemotherapy.

Before the mature results of the GOG-111 trial became available, the Gynecologic Oncology Group (GOG) opened protocol #132, which was a three-armed randomized trial of cisplatin versus paclitaxel versus the combination of both drugs (11). This study did not demonstrate superiority for any of the three regimens. However, further analysis revealed that 47% of all patients were treated with other regimens prior to clinical progression because of persistent disease determined either clinically or during reassessment surgery. In the majority of patients randomized to cisplatin alone, subsequent therapy included paclitaxel; in the majority of patients randomized to paclitaxel alone, subsequent therapy included a platinum-containing regimen. One explanation for the conflicting results between GOG-132 and the other two trials (Intergroup and GOG-111) is that treatment crossovers, particularly those prior to clinical progression, account for the lack of difference in survival between patients randomized to paclitaxel-containing and non-paclitaxel-containing treatments. This study has, therefore, been interpreted as a trial of sequential platinum-paclitaxel chemotherapy versus concurrent platinum/paclitaxel chemotherapy.

Centres participating in the ICON3 trial were allowed to choose one of two control arms (carboplatin alone or CAP), making it in effect two parallel trials (10). When the full results of this
trial become available, it will provide evidence on the survival benefits of paclitaxel plus carboplatin versus carboplatin alone.

**Update**

In August 2002, a full report of the ICON3 trial was published in the *Lancet* (1u). As mentioned previously, the ICON3 trial compared paclitaxel plus carboplatin to both carboplatin alone and CAP. This is the largest trial published to date, with over 2000 women included in the trial. The ICON3 trial did not detect significant difference in overall survival between the paclitaxel plus carboplatin group and the control groups (p=0.74). These results need to be interpreted with caution because the ICON3 trial included patients with all stages of disease, while the other trials presented only included patients with advanced stage disease. Twenty percent of the patients (n=413) included in the ICON3 trial were diagnosed with stage I or II disease. Given the discrepancy between the results of ICON3 and the GOG and intergroup studies, the Gynecology DSG recommends caution when interpreting the results.

An abstract reported the results of a RCT which randomized 1,077 women with advanced ovarian cancer to receive either paclitaxel and carboplatin or docetaxel and carboplatin (SCOTROC trial) (9u). After a median follow-up of 23 months, there was no difference between the paclitaxel plus carboplatin arm and the docetaxel plus carboplatin arm in terms of progression-free survival (15.4 months versus 15.1 months, respectively) and two-year overall survival (69.8% and 65.4%, respectively). However, it is important to note that the data are still maturing, and that further follow-up was required to confirm the results.

Two abstracts reported the results of RCTs comparing paclitaxel and carboplatin with or without epirubicin (10u, 11u). Neither RCT reported a significant difference in progression-free survival. In one of the RCTs (N=887) median overall survival had not been reached (10u), however, in the other RCT (N=1282), there was no significant difference in median overall survival (11u).

**Table 2. Randomized trials of platinum plus paclitaxel as first-line chemotherapy for ovarian cancer.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Interventions</th>
<th>Median survival (months)</th>
<th>Hazard Ratio for mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG-111, 1996 (3)</td>
<td>Stage III &amp; IV suboptimal</td>
<td>- paclitaxel (135 mg/m² over 24 hours) + cisplatin (75 mg/m²)</td>
<td>38</td>
<td>Relative risk: 0.6 (0.5 to 0.8) p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>N=386</td>
<td>- cyclophosphamide + cisplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intergroup, 2000 (12)</td>
<td>Stages IIb-IV</td>
<td>- paclitaxel (175 mg/m² over 3 hours) + cisplatin (75 mg/m²)</td>
<td>36</td>
<td>0.73* (0.60 to 0.89) p=0.0016</td>
</tr>
<tr>
<td></td>
<td>N=680</td>
<td>- cyclophosphamide + cisplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG-132, 2000 (11)</td>
<td>Stage III &amp; IV suboptimal</td>
<td>- paclitaxel (135 mg/m² over 24 hours) + cisplatin (75 mg/m²)</td>
<td>26</td>
<td>0.99 (0.8 to 1.23)</td>
</tr>
<tr>
<td></td>
<td>N=614</td>
<td>- paclitaxel (200 mg/m² over 24 hours)</td>
<td>26</td>
<td>1.15 (0.93 to 1.42) p&lt;0.015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- cisplatin (100 mg/m²)</td>
<td>30</td>
<td>1.0 (p=0.31)</td>
</tr>
<tr>
<td>ICON3, 2000 (10)</td>
<td>Stages I-IV</td>
<td>- paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=6)</td>
<td>not reported**</td>
<td>0.93 (CI not reported)</td>
</tr>
</tbody>
</table>
(abstract) N=2074
- carboplatin alone
OR
cyclophosphamide + doxorubicin + cisplatin

p=0.73

**Update**

| Study          | Stage | N  | Treatment                                                                 | Median Survival | HR (95% CI) |
p |     |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ICON3, 2002 (1u)</td>
<td>I-IV</td>
<td>2074</td>
<td>paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=6)</td>
<td>36.1</td>
<td>0.98</td>
</tr>
</tbody>
</table>
|                |       |     | - carboplatin alone
OR
cyclophosphamide (500 mg/m²) + doxorubicin (50 mg/m²) + cisplatin (50 mg/m²) |                 | p=0.74     |
| SCOTROC, 2003 (9u) | IC-IV | 1077 | paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=5)                  | PFS*** NR       | 15.4       |
|                |       |     | - docetaxel (75 mg/m² over 1 hour) + carboplatin (AUC=5)                   |                 | 15.1       |
| Kristensen, 2004 (10u) | IIb-IV | 887 | paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=5)                  | PFS*** NR       | 16.3       |
|                |       |     | - paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=5) + epirubicin (75 mg/m²) |                 | 17.2       |
| Du Bois, 2004 (11u) | IIb-IV | 1282 | paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=5)                  |                 | 41.0       |
|                |       |     | - paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=5) + epirubicin (60 mg/m²) |                 | 45.8       |

* adjusted for age, performance status, stage, histologic type and grade, and residual disease
** 2-year survival rates were 64% with paclitaxel + carboplatin versus 62% in the control group
*** Median overall survival has not been reached.

AUC = area under the curve

**Single-agent versus Multi-agent Platinum-based Chemotherapy**

There is no conclusive evidence that multi-agent chemotherapy is associated with better survival rates than single-agent chemotherapy; however, the data available are from studies conducted before the introduction of paclitaxel.

For a paper published in 1998, the Advanced Ovarian Trialists' Group pooled individual-patient data from 1095 women who participated in nine randomized trials of single-agent versus multi-agent platinum-based chemotherapy, without paclitaxel (7). They did not detect a significant benefit for combination chemotherapy over single-agent treatment and reported a mortality hazard ratio of 0.91 (95% CI, 0.80 to 1.05; p=0.21) with the direction of the difference favouring combination therapy. The ICON2 trial (17), published after completion of the meta-analysis, compared carboplatin (area under the curve [AUC]=5) to cisplatin (50 mg/m²) + cyclophosphamide + doxorubicin. The median survival was 33 months in both arms (Mortality HR, 1.0; 95% CI, 0.86 to 1.16; p=0.98).

None of the trials described in the paragraph above, including ICON2, used paclitaxel as part of the multi-agent chemotherapy regimen. Important evidence will be available from the ICON3 trial, which compared single-agent carboplatin with carboplatin plus paclitaxel, but survival data from this comparison have not yet been published. This trial is listed with other ongoing trials in Section VI below.
The Role of Anthracyclines

The magnitude of the survival benefit from adding anthracyclines to chemotherapy is unclear. A meta-analysis of individual-patient data from four large studies that examined the addition of doxorubicin to cisplatin/cyclophosphamide (CP), published in 1991 by the Ovarian Cancer Meta-analysis Project, detected a statistically significant survival benefit for cyclophosphamide plus doxorubicin (Adriamycin) plus cisplatin (CAP) over CP (9). Despite the fact that none of the individual trials had detected a significant survival advantage for CAP over CP, pooled data from 1194 patients detected a 15% reduction in the odds of death in favour of CAP (p=0.02). Because the dose intensity of CAP was greater than that for CP in three of the four randomized trials, it is unclear to what extent the benefit of CAP was from a greater dose intensity versus the doxorubicin itself.

Carboplatin versus Cisplatin

No differences in survival rates have been detected in randomized trials of carboplatin versus cisplatin. In 1998, the Advanced Ovarian Trialists’ Group pooled individual-patient data from 2219 women with ovarian cancer who participated in 12 randomized trials of carboplatin versus cisplatin, as either single-agent chemotherapy or as part of multi-agent chemotherapy (7). They did not detect any difference in survival between carboplatin- and cisplatin-based first-line chemotherapy (HR, 1.02; 95% CI, 0.93 to 1.12; p=0.66; where a hazard ratio >1 favours cisplatin). None of the trials included in the meta-analysis used paclitaxel in the treatment regimens evaluated.

Table 3 lists 11 randomized studies that have evaluated the role of cisplatin versus carboplatin as the platinum agent in first-line chemotherapy for ovarian cancer (16,18-24,39-41). Nine of these (19-24,39-41) were included in the meta-analysis by the Advanced Ovarian Trialists’ Group (7); three other RCTs included in the meta-analysis did not provide survival data in published reports and are not described here (27,42,43).

There are also two trials of carboplatin plus paclitaxel versus cisplatin plus paclitaxel that were published after the meta-analysis (16,18), one of which was reported in abstract form (16). Neither of these trials detected a statistically significant difference in survival between cisplatin plus paclitaxel and carboplatin plus paclitaxel.

Update

The AGO-OVAR3 trial reported by du Bois et al (7u) stratified 798 women with stage IIb-IV ovarian cancer into two groups based on tumour size and stage; then the women were randomized to receive either paclitaxel with cisplatin or paclitaxel with carboplatin. Treatment arms were similar in terms of overall survival and progression-free survival. In terms of toxicity, there was more hematologic toxicity associated with the paclitaxel/carboplatin arm than the paclitaxel/cisplatin arm, however there was more gastrointestinal and neurologic toxicity associated with the paclitaxel/cisplatin arm than the paclitaxel/carboplatin arm (Tables 4b and 5b).

Similar to the AGO-OVAR3 trial (7u), the RCT by Ozols et al (8u) randomized women with advanced stage ovarian cancer (stage III, N=792) to receive either paclitaxel with cisplatin or paclitaxel with carboplatin. Ozols et al reported the results of Gynecologic Oncology Group study 158 (GOG-158). The results of GOG-158 from an abstract were described in the original guideline (26). Ozols et al also did not detect significant differences between groups in terms of overall survival and progression-free survival. Neurologic toxicity (grade 2 to 4) was similar between the treatment arms. Patients treated with paclitaxel/cisplatin experienced significantly more leukopenia, gastrointestinal, renal, and metabolic toxicity (grade 3 or 4) compared to the patients treated with paclitaxel/carboplatin. The patients treated with paclitaxel/carboplatin experienced significantly more thrombocytopenia (grade 3 or 4) than did patients treated with paclitaxel/cisplatin (Tables 4b and 5b). The RCT by Ozols et al did not report quality of life data.
Table 3. Randomized trials of carboplatin (+/- cyclophosphamide or paclitaxel) versus cisplatin (+/- cyclophosphamide or paclitaxel) as first-line chemotherapy for ovarian cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Interventions</th>
<th>Median survival (months)</th>
<th>Hazard Ratio for mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson, 1988 (39)</td>
<td>Stage IIb - IV N=39</td>
<td>cisplatin (100 mg/m²) + cyclophosphamide carbo platinum (300 mg/m²) + cyclophosphamide</td>
<td>22</td>
<td>not reported</td>
</tr>
<tr>
<td>GONO, 1991 (19)</td>
<td>Stage III - IV N=164</td>
<td>cisplatin (50 mg/m²) + doxorubicin + cyclophosphamide carbo platinum (200 mg/m²) + doxorubicin + cyclophosphamide</td>
<td>23</td>
<td>not reported p&gt;0.05</td>
</tr>
<tr>
<td>GICOG, 1989 (20)</td>
<td>Stage III - IV N=167</td>
<td>cisplatin (100 mg/m²) carbo platinum (400 mg/m²)</td>
<td>31</td>
<td>not reported p=0.10</td>
</tr>
<tr>
<td>Mayo, 1989 (40)</td>
<td>Stage III - IV N=103</td>
<td>cisplatin (60 mg/m²) + cyclophosphamide carbo platinum (150 mg/m²) + cyclophosphamide</td>
<td>27</td>
<td>Relative risk: 2.18 (1.14 to 4.19) p=0.14</td>
</tr>
<tr>
<td>Adams, 1989 (21)</td>
<td>Stage IIb-III N=80</td>
<td>cisplatin (100 mg/m²) carbo platinum (400 mg/m²)</td>
<td>18</td>
<td>not reported p&gt;0.05</td>
</tr>
<tr>
<td>SWOG, 1992 (22)</td>
<td>Stage IIIc suboptimal &amp; stage IV N=291</td>
<td>cisplatin (100 mg/m²) + cyclophosphamide carbo platinum (300 mg/m²) + cyclophosphamide</td>
<td>17</td>
<td>0.99 (0.77 to 1.29) p&gt;0.05</td>
</tr>
<tr>
<td>NCIC, 1992 (23)</td>
<td>Stage III &amp; IV N=417</td>
<td>cisplatin (75 mg/m²) + cyclophosphamide carbo platinum (300 mg/m²) + cyclophosphamide</td>
<td>25</td>
<td>not reported p=0.81</td>
</tr>
<tr>
<td>Taylor, 1994 (41)</td>
<td>Stage III &amp; IV N=131</td>
<td>cisplatin (100 mg/m²) carbo platinum (400 mg/m²)</td>
<td>20</td>
<td>not reported p&gt;0.05</td>
</tr>
<tr>
<td>GOCA, 1997 (24)</td>
<td>Stage III &amp; IV N=173</td>
<td>cisplatin (80 mg/m²) + cyclophosphamide carbo platinum (350 mg/m²) + cyclophosphamide</td>
<td>35</td>
<td>Relative risk: 0.86 (0.55 to 1.34) p=0.99</td>
</tr>
<tr>
<td>Dutch/Danish, 2000 (18)</td>
<td>Stage IIb-IV N=208</td>
<td>cisplatin (75 mg/m²) + paclitaxel (175 mg/m² over 3 hours) carbo platinum (AUC=5) + paclitaxel (175 mg/m² over 3 hours)</td>
<td>not reported</td>
<td>0.85 (0.59 to 1.24) p&gt;0.05</td>
</tr>
<tr>
<td>AGO OVAR-3, 1999 (16) (abstract)</td>
<td>Stage IIb-IV N=776</td>
<td>cisplatin (75 mg/m²) + paclitaxel (185 mg/m² over 3 hours) carbo platinum (AUC=6) + paclitaxel (185 mg/m² over 3 hours)</td>
<td>not reached</td>
<td>not reported p=0.47</td>
</tr>
</tbody>
</table>

**Update**

du Bois, Stages IIb-IV - paclitaxel (185 mg/m² over 3 hours) 43.3
Pooling Survival Data from RCTs

High-quality meta-analyses addressing the efficacy of platinum, the use of single-agent versus multi-agent chemotherapy, the relative merits of carboplatin and cisplatin, and the role of anthracyclines in the first-line treatment of ovarian cancer have been published in the medical literature (7-9).

No meta-analysis of paclitaxel-based first-line therapy was found, but full reports with survival curves were available for three RCTs (3,11,12). The guideline authors considered pooling data from these three studies in order to estimate the overall effect on survival of paclitaxel plus platinum. Pooling was not performed because of differences in the study populations (stage of disease), control groups, doses and infusion times. One trial (GOG 132) was, in effect, a trial of concurrent platinum/paclitaxel chemotherapy versus sequential platinum-paclitaxel chemotherapy (11). Please see page 5 for further information and an interpretation of the GOG 132 trial results (11). Two other trials compared paclitaxel plus cisplatin with cyclophosphamide plus cisplatin (3,12), but one of these allowed consolidation treatment and interval debulking (12).

Toxicity/Adverse Effects

Cisplatin versus Carboplatin

There is evidence from randomized trials of significant differences in acute toxicity between carboplatin and cisplatin (18-27,29). Where data were available from all or most trials, rates of acute grade 3 or 4 adverse effects were pooled by the guideline authors and appear in the last row of Tables 4a and 5a. The pooled results are expressed as risk ratios (RR) where a risk ratio <1.0 favours cisplatin and a RR >1.0 favours carboplatin.

While hematologic adverse effects (Table 4a) were more frequent with carboplatin than with cisplatin (RR, 0.19; 95% CI, 0.14 to 0.25, for grade 3 or 4 thrombocytopenia), non-hematologic adverse effects (Table 5a) were more frequent with cisplatin (RR for grade 3/4 nausea & vomiting, 1.63; 95% CI, 1.28 to 2.07; RR for neurotoxicity, 2.40; 95% CI, 1.67 to 3.45). Data on renal toxicity were reported for seven trials (18-23,27). Grade 3 or 4 renal toxicity was reported in only two of 631 women treated with cisplatin and in none of those who received carboplatin.

It should be noted that there was significant statistical heterogeneity among the studies. Overall risk ratios similar to those noted in Tables 4a and 5a were obtained when the meta-analysis was restricted to trials with paclitaxel in both arms (18,25,26,29).

The Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) study group evaluated the long-term effects of first-line chemotherapy and reported in an abstract that 41% of patients had some degree of neuropathy 12 months after completing treatment with cisplatin plus paclitaxel, in contrast with 18% of those treated with carboplatin plus paclitaxel. At 24 months of follow-up, neuropathy was present in 13% of the cisplatin/paclitaxel group but none of the carboplatin/paclitaxel group (29).

Table 4a. Hematologic toxicity data from randomized trials of carboplatin versus cisplatin as first-line chemotherapy for ovarian cancer: percentage of patients experiencing grade 3 or 4 acute adverse effects.

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Stage</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>AUC 1</th>
<th>AUC 2</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>(7u)</td>
<td></td>
<td>+ carboplatin (AUC=6)</td>
<td>- paclitaxel (185 mg/m² over 3 hours) + cisplatin (75 mg/m²)</td>
<td>44.1</td>
<td></td>
<td>1.045</td>
<td>(0.869-1.257)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=7.5)</td>
<td></td>
<td>57.4</td>
<td>0.84</td>
<td>(0.70-1.02)</td>
</tr>
<tr>
<td></td>
<td>(8u)</td>
<td>Stage III</td>
<td>+ carboplatin (AUC=7.5)</td>
<td>- paclitaxel (135 mg/m² over 24 hours) + cisplatin (75 mg/m²)</td>
<td></td>
<td>48.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AUC = area under the curve
<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Grade 3/4 leukopenia</th>
<th>Grade 3/4 thrombocytopenia</th>
<th>Grade 3/4 anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>GONO, 1988 (19)</td>
<td>cisplatin (50 mg/m²) + doxorubicin + cyclophosphamide</td>
<td>41%</td>
<td>1%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>carboplatin (200 mg/m²) + doxorubicin + cyclophosphamide</td>
<td>46%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>GICOG, 1989 (20)</td>
<td>cisplatin (100 mg/m²)</td>
<td>0</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>carboplatin (400 mg/m²)</td>
<td>4%</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Adams, 1989 (21)</td>
<td>cisplatin (100 mg/m²)</td>
<td>0</td>
<td>0</td>
<td>not reported</td>
</tr>
<tr>
<td></td>
<td>carboplatin (400 mg/m²)</td>
<td>3%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>SWOG, 1992 (22)</td>
<td>cisplatin (100 mg/m²) + cyclophosphamide</td>
<td>66%</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>carboplatin (300 mg/m²) + cyclophosphamide</td>
<td>74%</td>
<td>24%</td>
<td>3%</td>
</tr>
<tr>
<td>NCIC, 1992 (23)</td>
<td>cisplatin (75 mg/m²) + cyclophosphamide</td>
<td>78%</td>
<td>6%</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>carboplatin (300 mg/m²) + cyclophosphamide</td>
<td>82%</td>
<td>41%</td>
<td>42%</td>
</tr>
<tr>
<td>GOCA, 1997 (24)</td>
<td>cisplatin (80 mg/m²) + cyclophosphamide</td>
<td>56%</td>
<td>9%</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>carboplatin (350 mg/m²) + cyclophosphamide</td>
<td>65%</td>
<td>33%</td>
<td>11%</td>
</tr>
<tr>
<td>Dutch/Danish, 2000 (18)*</td>
<td>cisplatin (75 mg/m²) + paclitaxel (175 mg/m² over 3 hours)</td>
<td>50%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>carboplatin (AUC 5) + paclitaxel (175 mg/m² over 3 hours)</td>
<td>71%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>AGO - OVAR3, 1999 (29)</td>
<td>cisplatin (75 mg/m²) + paclitaxel (185 mg/m² over 3 hours)</td>
<td>8%</td>
<td>&gt;1%</td>
<td>not reported</td>
</tr>
<tr>
<td>(abstract)</td>
<td>carboplatin (AUC 6) + paclitaxel (185 mg/m² over 3 hours)</td>
<td>14%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>GOG-158, 1999 (26)</td>
<td>cisplatin (75 mg/m²) + paclitaxel (135 mg/m² over 24 hours)</td>
<td>12%</td>
<td>5%</td>
<td>not reported</td>
</tr>
<tr>
<td>(abstract)</td>
<td>carboplatin (AUC 7.5) + paclitaxel (175 mg/m² over 3 hours)</td>
<td>6% (grade 4)</td>
<td>39%</td>
<td></td>
</tr>
</tbody>
</table>

Overall RR for adverse event (95% CI); RR <1.0 favours cisplatin

<table>
<thead>
<tr>
<th></th>
<th>0.88 (0.74 to 1.03)</th>
<th>0.19 (0.14 to 0.25)</th>
<th>not calculated</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2999</td>
<td>3000</td>
<td></td>
</tr>
</tbody>
</table>

* during the first six cycles of treatment

AUC = area under the curve
### Table 4b. Hematologic toxicity data from randomized trials of carboplatin versus cisplatin as first-line chemotherapy for ovarian cancer: percentage of patients experiencing grade 3 or 4 acute adverse effects

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Grade 3/4 leukopenia</th>
<th>Grade 3/4 thrombocytopenia</th>
<th>Grade 3/4 anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGO OVAR3, 2003 (7u)</td>
<td>cisplatin (75 mg/m²) + paclitaxel (185 mg/m² over 3 hours)</td>
<td>10.8%</td>
<td>1.0%</td>
<td>10.5%</td>
</tr>
<tr>
<td></td>
<td>carboplatin (AUC 6) + paclitaxel (185 mg/m² over 3 hours)</td>
<td>31.9%</td>
<td>12.9%</td>
<td>18.3%</td>
</tr>
<tr>
<td>Ozols, 2003 (8u)</td>
<td>paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=7.5)</td>
<td>63%</td>
<td>39%</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>paclitaxel (135 mg/m² over 24 hours) + cisplatin (75 mg/m²)</td>
<td>59%</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>
Table 5a. Non-hematologic toxicity data from randomized trials of carboplatin versus cisplatin as first-line chemotherapy for ovarian cancer: percentage of patients experiencing grade 3 or 4 acute adverse effects.

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Grade 3/4 nausea &amp; vomiting</th>
<th>Grade 3/4 neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>GONO, 1991 (19)</td>
<td>Cisplatin (50 mg/m²) + doxorubicin + cyclophosphamide</td>
<td>73%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Carboplatin (200 mg/m²) + doxorubicin + cyclophosphamide</td>
<td>63%</td>
<td>0</td>
</tr>
<tr>
<td>EORTC, 1988 (27)</td>
<td>Cisplatin (20 mg/m²) + doxorubicin + cyclophosphamide + hexamethylmelamine</td>
<td>74%</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Carboplatin (350 mg/m²) + doxorubicin + cyclophosphamide + hexamethylmelamine</td>
<td>60%</td>
<td>0</td>
</tr>
<tr>
<td>GICOG, 1989 (20)</td>
<td>Cisplatin (100 mg/m²)</td>
<td>7%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Carboplatin (400 mg/m²)</td>
<td>2%</td>
<td>0</td>
</tr>
<tr>
<td>Adams, 1989 (21)</td>
<td>Cisplatin (100 mg/m²)</td>
<td>not reported</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Carboplatin (400 mg/m²)</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>SWOG, 1992 (22)</td>
<td>Cisplatin (100 mg/m²) + cyclophosphamide</td>
<td>17%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Carboplatin (300 mg/m²) + cyclophosphamide</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>NCIC, 1992 (23)</td>
<td>Cisplatin (75 mg/m²) + cyclophosphamide</td>
<td>15%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Carboplatin (300 mg/m²) + cyclophosphamide</td>
<td>12%</td>
<td>0</td>
</tr>
<tr>
<td>GOCA, 1997 (24)</td>
<td>Cisplatin (80 mg/m²) + cyclophosphamide</td>
<td>57%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Carboplatin (350 mg/m²) + cyclophosphamide</td>
<td>33%</td>
<td>0</td>
</tr>
<tr>
<td>Dutch/Danish, 2000 (18)*</td>
<td>Cisplatin (75 mg/m²) + paclitaxel</td>
<td>17%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Carboplatin (AUC 5) + paclitaxel</td>
<td>14%</td>
<td>2%</td>
</tr>
<tr>
<td>AGO - OVAR3, 1999 (25) (abstract)</td>
<td>Cisplatin (75 mg/m²) + paclitaxel</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>Carboplatin (AUC 6) + paclitaxel</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>GOG-158, 1999 (26) (abstract)</td>
<td>Cisplatin (75 mg/m²) + paclitaxel</td>
<td>23%</td>
<td>not reported</td>
</tr>
<tr>
<td></td>
<td>Carboplatin (AUC 7.5) + paclitaxel</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Overall RR for adverse event (95% CI) ; RR &gt;1.0 favours carboplatin</td>
<td>1.63 (1.28 to 2.07)</td>
<td>2.40 (1.67 to 3.45)</td>
<td></td>
</tr>
</tbody>
</table>

* during the first six cycles of treatment
AUC = area under the curve
Update

Table 5b. Non-hematologic toxicity data from randomized trials of carboplatin versus cisplatin as first-line chemotherapy for ovarian cancer: percentage of patients experiencing grade 3 or 4 acute adverse effects.

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Grade 3/4 nausea &amp; vomiting</th>
<th>Grade 3/4 neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGO - OVAR3, 2003 (7u)</td>
<td>cisplatin (75 mg/m²) + paclitaxel, carboplatin (AUC 6) + paclitaxel</td>
<td>24.7%</td>
<td>17.7%</td>
</tr>
<tr>
<td>Ozols, 2003 (8u)</td>
<td>- paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=7.5)</td>
<td>Not reported</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>- paclitaxel (135 mg/m² over 24 hours) + cisplatin (75 mg/m²)</td>
<td></td>
<td>8%</td>
</tr>
</tbody>
</table>

Inclusion of Paclitaxel in Platinum-based Chemotherapy

Toxicity data from recent randomized trials on the addition of paclitaxel to carboplatin or cisplatin are presented in Tables 6 and 7. Rates of grade 3 or 4 neutropenia, thrombocytopenia, nausea and vomiting, and neurotoxicity from the two trials (3,12) of paclitaxel/cisplatin versus cyclophosphamide/cisplatin were pooled by the guideline authors. The pooled results are expressed as risk ratios where a risk ratio <1.0 favours paclitaxel/cisplatin and a RR >1.0 favours cyclophosphamide/cisplatin. No statistically significant differences in grade 3 or 4 adverse effects were detected between cisplatin plus paclitaxel and cisplatin plus cyclophosphamide.

There was significantly more neutropenia with cisplatin plus paclitaxel than with cisplatin alone, and significantly more gastrointestinal and neurologic toxicity with cisplatin alone at a dose of 100 mg/m² versus cisplatin at a dose of 75 mg/m² combined with paclitaxel.

Granulocyte colony-stimulating factors do not appear to have been used as primary prophylaxis for neutropenia in any of these trials.

The high rate of neurotoxicity observed in the paclitaxel plus cisplatin arm of the Intergroup trial may be related to the dose of paclitaxel used: 71% of patients had the dose escalated to 200 mg/m² (12).

Ten deaths possibly related to treatment were reported among 386 participants in the GOG-111 trial (six in the cisplatin/cyclophosphamide group and four in the cisplatin/paclitaxel group) (3).

Update

The SCOTROC trial which compared paclitaxel and carboplatin to docetaxel and carboplatin reported that women receiving paclitaxel plus carboplatin reported significantly more neurotoxicity (p<0.001) and significantly less myelosuppression than the women receiving docetaxel plus carboplatin (p<0.001) (9u).

Two abstracts reported the results of RCTs comparing paclitaxel and carboplatin with or without epirubicin (10u, 11u); however, only one of these trials reported toxicity results (11u). The incidence of grade 3 and 4 neutropenia, nausea, emesis, and mucositis was significantly higher in the women receiving epirubicin compared to those who were not receiving epirubicin (p<0.01).
Table 6. Hematologic toxicity data from randomized trials of platinum plus paclitaxel as first-line chemotherapy for ovarian cancer: percentage of patients experiencing grade 3 or 4 adverse effects.

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Grade 3/4 neutropenia</th>
<th>Grade 3/4 thrombocytopenia</th>
<th>Grade 3/4 anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG-111, 1996 (3)</td>
<td>paclitaxel (135 mg/m² over 24 hours) + cisplatin (75 mg/m²)</td>
<td>92%</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>cyclophosphamide + cisplatin (75 mg/m²)</td>
<td>83%</td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td>Intergroup 2000 (12)*</td>
<td>paclitaxel (175 mg/m² over 3 hours) + cisplatin (75 mg/m²)</td>
<td>64%</td>
<td>2%</td>
<td>not reported</td>
</tr>
<tr>
<td></td>
<td>cyclophosphamide + cisplatin (75 mg/m²)</td>
<td>71%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Overall RR for adverse event (N=1053) (95% CI)</td>
<td>1.00 (0.82 to 1.22)</td>
<td>0.52 (0.20 to 1.32)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>GOG-132, 2000 (11)</td>
<td>paclitaxel (135 mg/m² over 24 hours) + cisplatin (75 mg/m²)</td>
<td>94%</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>paclitaxel (200 mg/m² over 24 hours) + cisplatin (75 mg/m²)</td>
<td>96%</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>cisplatin (100 mg/m²)</td>
<td>48%</td>
<td>5%</td>
<td>12%</td>
</tr>
<tr>
<td>Update</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICON3, 2002 (1u)</td>
<td>paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=6)</td>
<td>31%*** (includes all hematological effects)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>carboplatin alone OR cyclophosphamide (500 mg/m²) + doxorubicin (50 mg/m²) + cisplatin (50 mg/m²)</td>
<td>44%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>SCOTROC, 2003 (9u)</td>
<td>paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=5)</td>
<td>82%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>docetaxel (75 mg/m² over 1 hour) + carboplatin (AUC=5)</td>
<td>94% (p&lt;0.001)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kristensen, 2004 (10u)</td>
<td>paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=5)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=5) + epirubicin (75 mg/m²)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Du Bois, 2004 (11u)</td>
<td>paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=5)</td>
<td>56%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=5) + epirubicin (60 mg/m²)</td>
<td>76% (p&lt;0.0001)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

* during the first six cycles of treatment
** paclitaxel + cisplatin vs cisplatin, reviewer’s calculation
*** not all centres participating in the study reported hematological effects
Table 7. Non-hematologic toxicity data from randomized trials of platinum plus paclitaxel as first-line chemotherapy for ovarian cancer: percentage of patients experiencing acute grade 3 or 4 adverse effects.

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Grade 3/4 nausea &amp; vomiting</th>
<th>Grade 3/4 renal toxicity</th>
<th>Grade 3/4 neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG-111, 1996 (3)</td>
<td>paclitaxel (135 mg/m² over 24 hours) + cisplatin (75 mg/m²)</td>
<td>15%</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>cyclophosphamide + cisplatin (75 mg/m²)</td>
<td>11%</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Intergroup*, 2000 (12)</td>
<td>paclitaxel (175 mg/m² over 3 hours) + cisplatin (75 mg/m²)</td>
<td>13%</td>
<td>not reported</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>cyclophosphamide + cisplatin (75 mg/m²)</td>
<td>19%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Overall RR for adverse event (N=1060)</td>
<td></td>
<td>0.96 (0.50 to 1.86)</td>
<td>-</td>
<td>4.53 (0.20 to 103.49)</td>
</tr>
<tr>
<td>GOG-132, 2000 (11)</td>
<td>paclitaxel (135 mg/m² over 24 hours) + cisplatin (75 mg/m²)</td>
<td>18%</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>paclitaxel (200 mg/m² over 24 hours)</td>
<td>10%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>cisplatin (100 mg/m³)</td>
<td>33%</td>
<td>4%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>p=0.0005**</td>
<td></td>
<td>p=0.238**</td>
<td>p=0.026**</td>
</tr>
<tr>
<td>Update</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICON3, 2002 (1u)</td>
<td>paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=6)</td>
<td>8%***</td>
<td>not reported</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>carboplatin alone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR cyclophosphamide (500 mg/m²) + doxorubicin (50 mg/m³) + cisplatin (50 mg/m³)</td>
<td>9%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>23%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>SCOTROC, 2003 (9u)</td>
<td>paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=5)</td>
<td>NR</td>
<td>NR</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>docetaxel (75 mg/m² over 1 hour) + carboplatin (AUC=5)</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kristensen, 2004 (10u)</td>
<td>paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=5)</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=5) + epirubicin (75 mg/m³)</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Du Bois, 2004 (11u)</td>
<td>paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=5)</td>
<td>3%</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>paclitaxel (175 mg/m² over 3 hours) + carboplatin (AUC=5) + epirubicin (60 mg/m³)</td>
<td>7%</td>
<td>p=.004</td>
<td></td>
</tr>
</tbody>
</table>

* during the first six cycles of treatment
** paclitaxel + cisplatin vs cisplatin, reviewer’s calculation
*** no p-values were reported
In the GOG-111 study, 10% of the women in the cisplatin/cyclophosphamide group and 8% of the cisplatin/paclitaxel group did not complete six cycles of therapy because of adverse effects or patient refusal. Overall, 87% completed the paclitaxel/cisplatin regimen and 78% the cyclophosphamide/cisplatin regimen (3). In the GOG-132 trial, 17% on high-dose cisplatin failed to complete six cycles of treatment because of toxicity or patient refusal, in contrast to 4% on high-dose paclitaxel and 7% on paclitaxel plus cisplatin. Eighty-one percent of those on combination therapy, 71% on paclitaxel alone and 69% on cisplatin alone, completed treatment (11).

With respect to paclitaxel dose, the National Cancer Institute of Canada (NCIC) study in women with recurrent ovarian cancer demonstrated lower hematologic toxicity in patients randomized to the 3-hour regimen compared with the 24-hour infusion schedule (33). This study is discussed further on the next page.

**Anthracyclines**

Preliminary results from an AGO-GINECO Intergroup Trial, reported in abstract form, describe higher rates of adverse effects when epirubicin was added to paclitaxel/carboplatin (28). Grade 3 or 4 neutropenia occurred in 65% of patients who were treated with epirubicin (60 mg/m²) plus paclitaxel plus carboplatin versus 34% who received paclitaxel (175 mg/m² over 3 hours) plus carboplatin (area under the curve [AUC] 5). Rates for grade 3 or 4 thrombocytopenia were 14% with epirubicin versus 3% without, and for anemia they were 17% versus 4%.

**Quality of Life**

The randomized trials described above provide very little information on the effects of treatment on quality of life. Abstract reports of the AGO OVAR-3 trial state that quality of life during treatment with platinum plus paclitaxel, measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) 30 questionnaire, was "significantly inferior" with cisplatin compared to carboplatin (p<0.001) (25,29).

**Update**

The AGO-OVAR3 trial (7u) evaluated quality of life using the EORTC QLQ-C30 questionnaire. Patients completed the questionnaire after the last treatment cycle, then three months after treatment, and again at six months after treatment. Quality-of-life scores were significantly lower for the patients in the paclitaxel/cisplatin arm than for the women in the paclitaxel/carboplatin arm. The difference in the quality-of-life scores was greatest immediately after treatment; however, a similar trend continued after three and six months. It is important to note that not all patients completed the quality-of-life assessments; thus there may be bias in the results.

**Dose and Schedule of Administration of Platinum-based First-line Chemotherapy**

The doses and schedules used in the randomized trials of paclitaxel plus platinum summarized in this guideline report are listed in Appendix 4.

**Carboplatin**

Gore et al randomized 227 women with ovarian cancer to receive carboplatin at an AUC of 6 for six cycles or an AUC of 12 for four cycles (30). Overall survival rates at five years were 31% and 34%, respectively. The Danish Ovarian Cancer Group performed a similar randomized trial involving 222 women who were allocated to treatment with carboplatin at an AUC of 4 or 8 for six cycles (31). They observed no difference in crude survival rates between treatment groups (median survival time = 19 months for both).
**Cisplatin**

Ben-David et al pooled data from 21 randomized controlled trials and 17 cohort studies that used cisplatin- or carboplatin-based treatment (without paclitaxel) in at least one study arm (32). They detected no significant correlation between total dose-intensity of cisplatin and survival.

**Paclitaxel**

Indirect evidence on dose and schedule for paclitaxel is available from a randomized trial in 391 women with recurrent ovarian cancer by the NCIC, in cooperation with the EORTC (33). Using a 2x2 factorial design, this study evaluated doses of 135 mg/m² and 175 mg/m² given over 3 or 24 hours. While there was a statistically significant prolongation of median time to progression in the higher dose arm (19 weeks with 175 mg/m² versus 14 weeks with 135 mg/m², p=0.02), the clinical significance of this finding is subject to interpretation. There was no difference in time to progression between the infusion schedules (17 weeks with the 3-hour infusion versus 16 weeks with the 24-hour infusion). There were no significant differences in overall survival (p=0.8 for dose and p=0.9 for infusion schedule) or quality of life among the four treatment groups. Twelve percent of patients in the 24-hour infusion group experienced febrile neutropenia in contrast with none in the 3-hour infusion group (p<0.0001).

There have been no randomized studies of 3- versus 24-hour infusion schedules in first-line chemotherapy for ovarian cancer. The GOG-158 trial compared 135 mg/m² over 24 hours to 175 mg/m² over three hours but with a different platinum agent added to paclitaxel in each arm (26). Survival data are not available, but no significant difference in recurrence-free survival was detected between the two arms of the trial (HR, 0.91; 95% CI, 0.76 to 1.10).

**Number of Treatment Cycles**

Three randomized trials of platinum-based chemotherapy without paclitaxel have examined the optimal number of cycles of first-line chemotherapy (Table 8) (34-36), and one trial of platinum plus paclitaxel is ongoing. The North Thames Oncology Group compared 5 with 8 cycles of either cisplatin or carboplatin and detected no significant difference in survival between the two arms (34). Two similar studies using CAP as first-line treatment, one comparing 5 with 10 cycles at the Memorial Sloan-Kettering Cancer Centre (35) and another of 6 versus 12 cycles by the Danish Ovarian Study Group (36), detected no significant difference in overall survival between longer and shorter courses of treatment. Results are pending from the GOG-157 trial, a recently completed study evaluating 3 versus 6 cycles of carboplatin/paclitaxel in women with stage I or II ovarian cancer.
Table 8. Randomized trials of different numbers of cycles of platinum-based first-line chemotherapy for ovarian cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Interventions</th>
<th>Median survival (months)</th>
<th>P-value on difference between survival curves</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTOG, 1997</td>
<td>Stage Ic-IV N=233</td>
<td>- 5 cycles (carboplatin or cisplatin)  - 8 cycles (carboplatin or cisplatin)</td>
<td>24 24</td>
<td>0.53</td>
</tr>
<tr>
<td>MSKCC, 1992</td>
<td>Stages IIc-IV N=78</td>
<td>- 5 cycles (CAP)  - 10 cycles (CAP)</td>
<td>24 40</td>
<td>0.34</td>
</tr>
<tr>
<td>DACOVA, 1993</td>
<td>Stages III-IV N=202</td>
<td>- 6 cycles (CAP)  - 12 cycles (CAP)</td>
<td>23 27</td>
<td>0.45</td>
</tr>
</tbody>
</table>

CAP = cyclophosphamide plus doxorubicin plus cisplatin

**Intraperitoneal Chemotherapy**

One of three randomized trials that compared intraperitoneal (i.p.) platinum-based therapy with intravenous (i.v.) platinum-based therapy for ovarian cancer demonstrated a statistically significant survival benefit for intraperitoneal chemotherapy (13,14,15). Survival data are presented in Table 9.

Table 9. Randomized trials of intraperitoneal versus intravenous platinum as first-line chemotherapy for ovarian cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>Median survival (months)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberts, 1996</td>
<td>Stage III N=654</td>
<td>i.p. cisplatin + i.v. cyclophosphamide  i.v. cisplatin + i.v. cyclophosphamide</td>
<td>48 40</td>
<td>Hazard ratio: 0.77 (CI not reported) p=0.02</td>
</tr>
<tr>
<td>Polyzos, 1999</td>
<td>Stage III N=90</td>
<td>i.p. carboplatin + i.v. cyclophosphamide  i.v. carboplatin + i.v. cyclophosphamide</td>
<td>26 25</td>
<td>not reported p=NS</td>
</tr>
<tr>
<td>Markman, 2001</td>
<td>Stage III N=462</td>
<td>i.v. carboplatin + i.v. paclitaxel + i.p. cisplatin  i.v. paclitaxel + i.v. cisplatin</td>
<td>63 52</td>
<td>Relative risk: 0.81 (95% CI, 0.65 to 1.00) p=0.05 (1-tailed)</td>
</tr>
</tbody>
</table>

i.p. = intraperitoneal; i.v. = intravenous; CI = confidence interval; NS = not significant

Alberts et al conducted a test of the interaction of treatment and extent of residual disease and found that the effect of route of administration of cisplatin (i.p. versus i.v.) was not influenced by the extent of residual disease (p=0.93) (13). Seventy-three percent of the women in this trial had minimal residual disease (<0.5 cm); the remaining patients had residual tumours between 0.5 and 2 cm. In the study by Polyzos et al, 57% of patients had a residual tumour mass less than 2 cm and 43% 2 cm or more (14). All of the women in the trial by Markman et al had residual disease ≤1 cm (15).

The Alberts and Polyzos studies detected significantly more leuakopenia with intravenous administration, and more abdominal pain and transient dyspnea with intraperitoneal administration compared to the other route of administration. Markman et al reported more grade 3-4 neutropenia, thrombocytopenia, gastrointestinal toxicity, and metabolic toxicity with the experimental treatment, which included i.v. carboplatin at a dose of AUC = 9 every four weeks for two courses followed by
i.p. cisplatin at a dose of 100 mg/m² every three weeks for six courses. In the study by Alberts et al., there were two treatment-related deaths in the intraperitoneal group and none in the i.v. group (13). Polyzos reported three intra-abdominal complications among 44 patients undergoing intraperitoneal treatment (14). Two patients in each arm of the trial by Markman et al. died from causes attributed to chemotherapy (15).

Despite the evidence from the Alberts trial, there are many clinicians who question the efficacy of intraperitoneal chemotherapy. The Alberts and Polyzos studies used platinum plus cyclophosphamide (which is not the present-day standard regimen for advanced ovarian cancer). It is also important to note that only 58% of patients were able to complete six cycles of therapy in both arms of the Alberts study (13). The difference in overall survival between standard-dose i.v. cisplatin plus paclitaxel and moderately high-dose i.v. carboplatin followed by i.v. paclitaxel and i.p. cisplatin in the intergroup trial, recently reported by Markman et al., is of borderline statistical significance (15).

The theoretical benefits of intraperitoneal chemotherapy relate to the fact that it can penetrate several millimetres into tissue from the peritoneal cavity. It therefore seems plausible that those patients with microscopic and minimal residual disease (i.e., less than 0.5 cm) would stand to gain the most in terms of survival. However, in the Alberts study, median survival in that subgroup of patients was 51 months, only marginally better than all patients receiving intraperitoneal platinum. Finally, there is no question that the use of an intraperitoneal catheter and the associated problems with blockage, maldistribution, and infection are impediments to treatment compared to intravenous chemotherapy.

Fallopian Tube Carcinoma

No randomized trials of chemotherapy for fallopian tube carcinoma were found. However, seven reports of case series evaluating first-line chemotherapy with cisplatin + cyclophosphamide ± doxorubicin have been published (44-50). Median survival ranged from 22 to 58 months. Data were collected retrospectively for the majority of these reports (44,45,47,48,50).

Primary Peritoneal Carcinoma

No randomized trials of chemotherapy for primary peritoneal carcinoma were found. However, four reports of case series evaluating first-line platinum-based chemotherapy have been published (51-54). Median survival ranged from 17 to 32 months. Data were collected retrospectively in all of these studies.

V. INTERPRETIVE SUMMARY

There is evidence from two randomized trials to support the use of paclitaxel plus platinum as first-line therapy for ovarian cancer (3,12). Data from RCTs, including trials where carboplatin and cisplatin were administered with paclitaxel (16,18), failed to demonstrate a difference in efficacy between cisplatin and carboplatin, but randomized trials have shown that these two agents have different toxicity profiles. Given that hematological toxicity is greater with carboplatin than with cisplatin and adverse gastrointestinal and renal effects are more common with cisplatin, the assessment of a relative toxicity advantage for one agent over the other must be qualitative and subjective. Limited data from one randomized trial demonstrated that quality of life was better during treatment with carboplatin plus paclitaxel than with cisplatin plus paclitaxel.

Although no randomized trials have compared different doses of cisplatin, carboplatin, and paclitaxel in first-line therapy for ovarian cancer, experience gained from the use of these agents in RCTs suggests that the following doses are reasonable: 135 to 175 mg/m² of paclitaxel over 3 to 24 hours and carboplatin at AUC 5 to 6 or cisplatin at 75 mg/m². Randomized trials of cisplatin have generally used a dose of 75 mg/m² in combination with paclitaxel (3,11,12,16,18,26,29). Mature survival data are not yet available from trials of carboplatin plus paclitaxel, but the majority of these have used doses of carboplatin of AUC = 5 (18) or AUC = 6 (10,16). A randomized trial of carboplatin, given with cyclophosphamide, at doses bracketing the range used in the clinical trials...
of carboplatin plus paclitaxel, detected no difference in survival between AU C= 4 and AUC = 8 (31). Indirect evidence from a randomized trial of second-line therapy shows that paclitaxel at a dose of 175 mg/m² over 3 hours appears to be just as efficacious, with less hematologic toxicity, as the same dose given over 24 hours (33). In the same trial, paclitaxel at a dose of 175 mg/m² was associated with an increase in progression-free survival of five weeks but no survival advantage, compared with a dose of 135 mg/m². One of two randomized trials showing a survival benefit for platinum plus paclitaxel as first-line therapy used a paclitaxel dose of 135 mg/m² over 24 hours (3), and the other used 175 mg/m² over 3 hours (12).

There are randomized studies of cisplatin alone and in combination with other drugs of 5 versus 8, 5 versus 10, and 6 versus 12 cycles of treatment. None of these has detected a difference in survival between short and long treatment regimens. The optimum number of cycles of platinum plus paclitaxel has yet to be tested in randomized trials. Given the experience with cisplatin plus paclitaxel in recent trials of first-line treatment for ovarian cancer (3,11), it would be appropriate to use six to eight cycles as standard treatment.

While there are some data to suggest that single-agent carboplatin is as efficacious as platinum plus paclitaxel (10) and that intraperitoneal cisplatin may be more efficacious than intravenous cisplatin (13), this evidence is limited and comes from only one study in each case. Similarly, the use of anthracyclines has yet to be adequately addressed with respect to their addition to combination platinum/paclitaxel chemotherapy.

**Update**

While the results of ICON3 trial indicate that the addition of paclitaxel to carboplatin provides no survival advantage, and increases toxicity, the Gynecology DSG members are cautious in interpreting its results for the following reasons: ICON3 was run as four parallel studies in different regions of Europe and included all stages of ovarian cancer; in fact 20% of the patients were stages I and II. Also, some of the countries/centres did not provide data on toxicity. Furthermore, the selection of which of the two control groups was to be used was determined by the treating physician. Finally, its results are at odds with two other large randomized studies (3,12).

Table 10 compares the four RCTs that measured platinum plus paclitaxel. From the table, it is evident that the results cannot be pooled because of the variance in treatment regimens across studies. This table also exemplifies the differences between studies according to inclusion of stages (ICON3 allowed all stages, while the other three trials limited eligibility to advanced disease), location of study (which has implications according to standards regarding surgery, administration of drugs and surveillance), and toxicity information reported. ICON3 was the only trial to neglect to report some toxicities for the participants. Hematological and motor neuropathy toxicity data are not available for almost 40% of the participants in the ICON3 trial.
Table 10. Comparison of the four RCTs measuring platinum plus paclitaxel.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>386</td>
<td>680</td>
<td>614</td>
<td>2074</td>
</tr>
<tr>
<td>Stages included</td>
<td>Stages III, IV (suboptimal)</td>
<td>Stages IIb-IV</td>
<td>Stages III, IV (suboptimal)</td>
<td>Stages I-IV (20% stages I-II)</td>
</tr>
<tr>
<td>Location</td>
<td>United States</td>
<td>Europe, Canada</td>
<td>United States</td>
<td>Europe (4 parallel trials)</td>
</tr>
</tbody>
</table>
| Regimen                 | - paclitaxel + cisplatin | - paclitaxel + cisplatin | - paclitaxel + cisplatin | - paclitaxel + carboplatin +
cyclophosphamide +
cisplatin |
|                         | - cyclophosphamide +
cisplatin | - cyclophosphamide +
cisplatin | - paclitaxel | - carboplatin |
|                         |                   |                       | - cisplatin       | - cyclophosphamide +
doxorubicin + cisplatin |
| Outcome                 | Paclitaxel + cisplatin improves survival | Paclitaxel + cisplatin improves survival | Paclitaxel + cisplatin is preferred treatment | Carboplatin alone is as effective as paclitaxel +
carboplatin in terms of survival |
| Toxicity reports        | Reported for all participants | Reported for 99% patients | Reported for all participants | Italian centres (40% of participants) did not report all toxicities |

The SCOTROC trial (9u) comparing paclitaxel and carboplatin to docetaxel and carboplatin detected no difference in progression-free and overall survival between the two treatment groups. There was significantly more myelosuppression reported in the docetaxel and carboplatin arm compared to the paclitaxel and carboplatin arm, and there was significantly more neurotoxicity reported in the paclitaxel and carboplatin arm than the docetaxel and carboplatin arm. The results of this study have only been presented in abstract form at this time; however, as the data from this trial mature, the Gynecology Cancer DSG will review the evidence and update the guideline as necessary.

VI. ONGOING TRIALS
Closed Trials
The following trials have completed recruitment but have not yet published survival results:

**Italian study:** Phase II randomized study of the addition of ifosfamide or epirubicin to paclitaxel/cisplatin in women with stage II-IV ovarian cancer. Preliminary toxicity and tumour response data were presented at the 1999 ASCO meeting (55).

**AGOSG-OVAR-5:** Phase III randomized study of paclitaxel and carboplatin with or without epirubicin in patients with Stage IIb, III, or IV ovarian epithelial cancer. Preliminary toxicity data were presented at the 1999 IGCS meeting (28).

**GOG-162:** Phase III randomized study of 24-hour versus 96-hour infusion of paclitaxel with cisplatin in patients with suboptimal stage III or IV ovarian epithelial cancer or primary peritoneal cancer.

**GOG-172:** Phase III randomized study of i.v. paclitaxel and cisplatin versus i.v. paclitaxel, i.p. cisplatin and i.p. paclitaxel in patients with optimal stage III epithelial ovarian carcinoma or primary peritoneal carcinoma. Preliminary results were presented at the 2002 ASCO meeting (12u).
**CRC-BOC-SCOTROC, EU-99010:** Phase III randomized study of paclitaxel and carboplatin versus docetaxel and carboplatin in chemotherapy-naive patients with stage Ic-IV ovarian epithelial cancer.

**NSGO-OC9804:** Phase III randomized study of paclitaxel and carboplatin with or without epirubicin as initial treatment in patients with Stage IIb, III, or IV invasive ovarian epithelial, fallopian tube, or peritoneal cancer. Canadian centres are participating in this intergroup study through the NCIC Clinical Trials Group OV.14 trial.

**Open Trials**

According to the information available, the following trials are open for patient recruitment:

**CAN-NCIC-OV16, EORTC-55012, GEICO-0101:** Phase III Randomized Study of Cisplatin and Topotecan Followed By Paclitaxel and Carboplatin Versus Paclitaxel and Carboplatin Alone in Patients With Newly Diagnosed Stage IIIB-IV Ovarian Epithelial, Primary Peritoneal, or Fallopian Tube Cancer.

**GOG-0182, SWOG-G0182:** Phase III Randomized Study of Paclitaxel and Carboplatin with or without Gemcitabine, Doxorubicin HCl Liposome, or Topotecan in Patients with Stage III or IV Ovarian Epithelial or Primary Peritoneal Carcinoma.

**VII. DISEASE SITE GROUP CONSENSUS PROCESS**

After reviewing the first draft of the guideline report, there was consensus among the 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 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 AUC of 5-6,
- paclitaxel may be used in doses ranging from 135 to 175 mg/m² 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/m² over three hours with a dose of 135 mg/m² 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 DSG recommends that paclitaxel be administered as a three-hour infusion at a dose of either 135 to 175 mg/m².

- 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 Section VI above.

- 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 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.

Update

In November 2002, the Gynecology Cancer 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.

In June 2004, the Gynecology Cancer DSG met to discuss the results of the SCOTROC trial which compared paclitaxel and carboplatin to docetaxel and carboplatin (9u). The DSG concluded that, based on the results of the trial that indicate that there is no significant survival difference between the two treatments, that either is acceptable. The DSG acknowledged that there was a significant difference in the toxicity between the treatment arms: significantly more neurotoxicity among women treated with paclitaxel than docetaxel; however, there was significantly more myelosuppression among the women treated with docetaxel than paclitaxel.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

This section describes the external review activities undertaken for the original guideline report.

Draft Recommendations

Based on the evidence described in the original report, the Gynecology DSG drafted the following recommendations:
**Target Population**

These recommendations apply to postoperative patients with newly diagnosed stage II, III (with or without measurable disease after surgery) or IV epithelial ovarian cancer.

**Draft Recommendations**

- Intravenous carboplatin plus 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.
- Intravenous carboplatin as a single agent may be considered as a treatment option under the following circumstances:
  a) in patients for whom paclitaxel is contraindicated,
  b) in patients who are unwilling to accept the adverse effects of paclitaxel chemotherapy.

**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.

**Fallopian Tube Cancer and Primary Peritoneal Cancer**

Although there are no randomized trials of chemotherapy in fallopian tube cancer or primary peritoneal cancers, given that most clinicians treat these uncommon cancers as ovarian cancers, the authors of this guideline feel the recommendations made above can be applied to fallopian tube cancer and primary peritoneal cancer.

**Related Guidelines**

The Gynecology Disease Site Group is also developing an evidence summary on chemotherapy for recurrent epithelial ovarian cancer previously treated with platinum and plans to develop a guideline on the management of stage I ovarian cancer in the future. Radiotherapy, surgery, and neoadjuvant chemotherapy for stage II-IV ovarian cancer will be covered by separate guidelines.

**Practitioner Feedback**

Based on the evidence and the draft recommendations contained in the original report, feedback was sought from Ontario clinicians.

**Methods**

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 DSG reviewed the survey results.

**Results**

Thirty-six completed surveys were returned (66%). Twenty-nine (81%) respondents indicated that the practice-guideline-in-progress report was relevant to their clinical practice and completed the survey. Key results are summarized in Table 11.
Table 11. Practitioner responses to eight items on the feedback survey

<table>
<thead>
<tr>
<th>Item</th>
<th>Strongly agree or agree</th>
<th>Neither agree nor disagree</th>
<th>Strongly disagree or disagree</th>
<th>Number Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing a clinical practice guideline, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>29 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>28 (97%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>28 (97%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>29 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>29 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>29 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>25 (96%)</td>
<td>1 (4%)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?</td>
<td>28 (100%)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Summary of Written Comments

Nine respondents (31%) provided written comments. The main points made in the written comments were:
1. The treatment recommended by these guidelines has already become the standard treatment in some centres.
2. The report advises that paclitaxel may be given at a dose of at 135-175mg/m² over 3 hrs, but one practitioner provided feedback that he/she would not give 135mg/m² over 3 hours but only over 24 hours.
3. The optimal number of cycles of treatment remains an issue.
4. One practitioner alerted the Gynecology DSG to the fact that the results of the ICON3 study (available only in abstract form at the time that the guideline was developed) had been submitted for publication. The results of this trial may help to clarify whether or not carboplatin plus paclitaxel is superior to carboplatin alone.

Modifications/Actions

The practice guideline recommendations were not changed as a result of this feedback. The limited evidence available on dose and duration of treatment had already been described in the guideline report. The DSG will update the evidence from the ICON3 trial as soon as it is published.

Feedback from the Practice Guidelines Coordinating Committee

Following practitioner feedback, the practice guideline was reviewed by the Practice Guidelines Coordinating Committee (PGCC). In response to feedback from the Coordinating Committee, the Gynecology DSG 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.

Approved Practice Guideline Recommendations
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 Gynecology DSG and the PGCC.

**Recommendations**
- Intravenous carboplatin plus 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.
- Intravenous carboplatin as a single agent may be considered as a treatment option under the following circumstances:
  a) in patients for whom paclitaxel is contraindicated,
  b) in patients who are unwilling to accept the adverse effects of paclitaxel chemotherapy.

**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.

**Update**
Since the completion of the original guideline, the ICON3 trial, a randomized trial that compared paclitaxel plus carboplatin versus carboplatin alone versus cyclophosphamide, doxorubicin, and cisplatin, has been fully published. The results of the ICON3 trial modify the recommendations of this guideline because the ICON3 trial did not detect a difference in survival among the three treatment groups. The change in the recommendations was not circulated for external review because the modified recommendations do not deviate substantially from the original recommendations. The current recommendations are as follows:

**Recommendations Update**
- 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.

**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 can be used without paclitaxel is based on the results of one large randomized study (ICON3). There are some important differences between the ICON3 trial and the other RCTs (outlined in the Interpretive Summary).

**IX. PRACTICE GUIDELINE**
This practice guideline reflects the most current information reviewed by the Gynecology DSG.

**Target Population**
These recommendations apply to postoperative patients 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.

**Recommendations Update**

- Intravenous carboplatin with or without paclitaxel or docetaxel is the recommended postoperative chemotherapy regimen for newly diagnosed stage II-IV epithelial ovarian cancer.
  - Paclitaxel in combination with carboplatin is associated with greater neurotoxicity than docetaxel and carboplatin, however, the combination of docetaxel and carboplatin is associated with more myelosuppression than paclitaxel and carboplatin. The differences in the toxicity profiles should be discussed with patients when choosing the most appropriate regimen.

- Intravenous cisplatin plus paclitaxel may also be considered as a treatment option.

**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 can be used without paclitaxel is based on the results of one large randomized study (ICON3). There are some important differences between the ICON3 trial and the other RCTs (outlined in the Interpretive Summary).
- The recommendation that either paclitaxel or docetaxel is acceptable to be used in combination with carboplatin is based on the results of a randomized trial that compared docetaxel and carboplatin to paclitaxel and carboplatin. Survival data indicate that there is not a significant difference in progression-free and overall survival between the two treatment groups. There was significantly more myelosuppression reported in the docetaxel and carboplatin arm compared to the paclitaxel and carboplatin arm, and there was significantly more neurotoxicity reported in the paclitaxel and carboplatin arm than the docetaxel and carboplatin arm.

**Dose and Schedule of Administration**

Although no randomized trials have compared different doses of cisplatin, carboplatin or paclitaxel in first-line therapy for ovarian cancer, experience gained from the use of these agents in randomized trials suggests that the following doses are reasonable: 135 to 175 mg/m² of paclitaxel over three hours, and carboplatin at AUC 5 to 6 or cisplatin at 75 mg/m².

**Fallopian Tube Cancer and Primary Peritoneal Cancer**

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 authors of this guideline feel the recommendations made above can be applied to fallopian tube and primary peritoneal cancers.

**Related Guidelines**

Practice Guidelines Initiative Evidence Summary Report #4-3: Chemotherapy for Recurrent Epithelial Ovarian Cancer Previously Treated with Platinum.

**X. JOURNAL REFERENCE**

This practice guideline report was originally completed on September 21, 2001 and published in 2002: Covens A, Carey M, Bryson P, Verma S, Fung Kee FM, Johnston M.

**XI. ACKNOWLEDGEMENTS**

The Gynecology Disease Site Group would like to thank Dr Allan Covens, Dr. Mark Carey, Dr. Peter Bryson, Dr. Shailendra Verma, Dr. Michael Fung Kee Fung, Ms. Alexandra Chambers and Ms. Mary Johnston for taking the lead in drafting, revising, and updating this practice guideline report.

*For a complete list of the Gynecology Disease Site Group members, please visit the CCO Web site at [http://www.cancercare.on.ca/](http://www.cancercare.on.ca/)*
REFERENCES


Update


Appendix 1. Literature search strategy (19 July 1999).

001 antineoplastic agents/
002 drug therapy/
003 exp drug therapy/
004 first-line chemotherapy.tw.
005 first line chemotherapy.tw.
006 chemotherapy.tw.
007 or/1-6
008 ovarian neoplasms/
009 ovarian neoplasm?.tw.
010 ovarian cancer.tw.
011 epithelial ovarian cancer.tw.
012 or/8-11
013 random:.sh,tw,pt.
014 7 and 12
015 13 and 14
016 phase iii.tw.
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018 controlled:.sh,tw,pt.
019 clinical trial?.sh,tw,pt.
020 (double-blind method: or single-blind method:).sh,tw.
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022 placebos/
023 or/18-22
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032 14 and 31
033 exp practice guidelines/
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036 (practice guideline or guideline?).tw,sh,pt.
037 consensus.sh,pt,pt.
038 or/33-37
039 14 and 38
040 letter.pt.
041 comment.pt.
042 editorial.pt.
043 or/40-42
044 low malignant potential tumours.tw.
045 low malignant potential tumors.tw.
046 low malignant potential tumor.tw.
047 or/44-46
048 cost:.sh,tw.
049 economic:.sh,tw.
050 health care rationing/
051 48 or 49 or 50
052 phase i.tw.
053 phase ii.tw.
054 52 or 53
055 stage i.tw.
056 43 or 47 or 54 or 55

057 14 and 51
058 15 or 17 or 24 or 57
059 32 or 39
060 limit 58 to yr=1980-1999
061 limit 59 to yr=1990-1999
062 60 or 61
063 62 not 56
064 limit 63 to human
065 limit 64 to english language

Stage I  Growth limited to the ovaries.
   Ia  Growth limited to one ovary; no ascites present containing malignant cells. No tumour on the external surface; capsule intact.
   Ib  Growth limited to both ovaries; no ascites present containing malignant cells. No tumour on the external surfaces; capsules intact.
   Ic  Tumour either Stage Ia or Ib, but with tumour on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings.

Stage II  Growth involving one or both ovaries with pelvic extension.
   IIa  Extension and/or metastases to the uterus and/or tubes.
   IIb  Extension to other pelvic tissues.
   IIc  Tumour either Stage IIa or IIb, but with tumour on surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.

Stage III  Tumour involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equals Stage III. Tumour is limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum.
   IIIa  Tumour grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces, or histologic-proven extension to small bowel or mesentery.
   IIIb  Tumour of one or both ovaries with histologically confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative.
   IIIc  Peritoneal metastasis beyond the pelvis > 2 cm in diameter and/or positive retroperitoneal or inguinal nodes.

Stage IV  Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to Stage IV. Parenchymal liver metastasis equals Stage IV.
Appendix 3. Acronyms used throughout this practice guideline report to describe randomized trials.

AGO = Arbeitsgemeinschaft Gynaekologische Onkologie
CRC = Cancer Research Campaign (Glasgow)
DACOVA = Danish Ovarian Study Group
GINECO = Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens
GOCA = German Ovarian Cancer Study Group
GOG = Gynecologic Oncology Group
GONO = Gruppo Oncologico Nord Ovest
GICOG = Gruppo Interregionale Cooperativo Oncologico Ginecologia
ICON = International Collaborative Ovarian Neoplasm Study
MSKCC = Memorial Sloan-Kettering Cancer Centre
NCIC = National Cancer Institute of Canada
NSGO = Nordic Society for Gynaecologic Oncology
NTOG = North Thames Oncology Group
SWOG = South West Oncology Group
Appendix 4. Doses and schedules of administration used in eight randomized controlled trials of intravenous platinum + paclitaxel as first-line chemotherapy for ovarian cancer.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Trials</th>
</tr>
</thead>
</table>
| Paclitaxel, 135 mg/m² over 24 hours + cisplatin, 75 mg/m² | - GOG-111, 1996 (3)  
- GOG-132, 2000 (11)  
- GOG-158 (25)* |
| Paclitaxel, 175 mg/m² over 3 hours + cisplatin, 75 mg/m² | - Intergroup, 2000 (12)  
- Dutch/Danish, 2000 (17)* |
| Paclitaxel, 185 mg/m² over 3 hours + cisplatin, 75 mg/m² | - AGO OVARG-3, 1999 (24,28)* |
| Paclitaxel, 175 mg/m² over 3 hours + carboplatin, AUC=5 | - Dutch/Danish, 2000 (17)*  
- AGO-GINECO, 1999 (27) |
| Paclitaxel, 175 mg/m² over 3 hours + carboplatin, AUC=6 | - ICON3, 2000 (10) |
| Paclitaxel, 185 mg/m² over 3 hours + carboplatin, AUC=6 | - AGO-OVAR-3, 1999 (24,28)* |
| Paclitaxel, 175 mg/m² over 3 hours + carboplatin, AUC=7.5 | - GOG-158 (25)* |

* two paclitaxel + platinum treatment arms

<table>
<thead>
<tr>
<th>Dose</th>
<th>Number of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel, 135 mg/m² over 24 hours</td>
<td>3 (GOG-111, GOG-132, GOG-158)</td>
</tr>
<tr>
<td>Paclitaxel, 175 mg/m² over 3 hours</td>
<td>5 (Intergroup, Dutch/Danish, AGO-GINECO, GOG-158, ICON3)</td>
</tr>
<tr>
<td>Paclitaxel, 185 mg/m² over 3 hours</td>
<td>1 (AGO OVARG-3)</td>
</tr>
<tr>
<td>Carboplatin, AUC=5</td>
<td>2 (Dutch/Danish, AGO-GINECO)</td>
</tr>
<tr>
<td>Carboplatin, AUC=6</td>
<td>2 (ICON3, AGO OVARG-3)</td>
</tr>
<tr>
<td>Carboplatin, AUC=7.5</td>
<td>1 (GOG-158)</td>
</tr>
<tr>
<td>Cisplatin, 75 mg/m²</td>
<td>6 (GOG-111, GOG-132, GOG-158, Intergroup, Dutch/Danish, AGO OVARG-3)</td>
</tr>
</tbody>
</table>

AUC = area under the curve
Evidence-based Series #4-1-2: Section 3

First-line Chemotherapy for Postoperative Patients with Stage II, III or IV Epithelial Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer

T. Le, N. Ismaila, and members of the Gynecology Cancer Disease Site Group

Guideline Review Summary

Review Date: November 29, 2012

The 2004 guideline recommendations are ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other informational purposes.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario’s Program in Evidence-based Care in 2001, and updated in 2004.

In September 2011, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (TL) reviewed and interpreted the new eligible evidence and proposed the existing recommendations should be archived. The Gynecology Cancer Disease Site Group (DSG) archived the recommendations found in Section 1 (Clinical Practice Guideline) in November 29, 2012.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

What is the optimal postoperative chemotherapy regimen for women with stage II, III (micro or macro) or IV epithelial ovarian cancer who are newly diagnosed and who have not previously received chemotherapy?

Literature Search and New Evidence

The new search (July 2004 to June 2012) yielded 27 references representing 2 meta-analysis, and 20 RCTs (1 RCT had 2 publications while 2 others had 3 publications), found evaluating the role first-line chemotherapy in postoperative patients with stage II, III or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. Only 1 of these RCTs is already included in the meta-analysis, while 19 references are potentially new studies. 17 of these new studies had full text publications while 2 were in abstract form. There
are 2 ongoing studies identified from clinicaltrials.gov. Brief results of these searches are shown in the Document Review Tool.

**Impact on Guidelines and Its Recommendations**
The Gynecology Cancer DSG ARCHIVED the 2004 recommendations on the role first-line chemotherapy in postoperative patients with stage II, III or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. Therefore this guideline will no longer be updated. The DSG will decide if and when a new document that will cover this topic will be produced.

### Document Review Tool

<table>
<thead>
<tr>
<th>Number and title of document under review</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-1-2 First-line Chemotherapy for Postoperative Patients with Stage II, III or IV Epithelial Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current Report Date</th>
<th>June 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Expert</td>
<td>Dr. Tien Le</td>
</tr>
<tr>
<td>Research Coordinator</td>
<td>Nofisat Ismaila</td>
</tr>
<tr>
<td>Date Assessed</td>
<td>September 2011</td>
</tr>
<tr>
<td>Approval Date and Review Outcome (once completed)</td>
<td>November 29, 2012 [ARCHIVE]</td>
</tr>
</tbody>
</table>

**Original Question(s):**
What is the optimal postoperative chemotherapy regimen for women with stage II, III (micro or macro) or IV epithelial ovarian cancer who are newly diagnosed and who have not previously received chemotherapy?

**Target Population:**
Postoperative patients 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.

**Study Section Criteria:**

**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 (RCT) 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 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.
Search Details:
- July 2004 to June 2012 (Medline May wk 5 + Embase week 23)
- July 2004 to June 2012 (ASCO Annual Meeting)
- July 2004 to June 2012 (Clinicaltrials.gov)

Brief Summary/Discussion of New Evidence:
Of 1177 total hits from Medline and Embase + 15 total hits from ASCO + 64 total hits from clinicaltrials.gov, 27 references representing 2 meta-analysis, and 20 RCTs (I RCT had 2 publications while 2 others had 3 publications), were found evaluating the role first-line chemotherapy in postoperative patients with stage II, III or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. Only 1 of these RCTs is already included in the meta-analysis, while 19 references are potentially new studies. 17 of these new studies had full text publications while 2 were in abstract form. There are 2 ongoing studies identified from clinicaltrials.gov.

### Systematic review and Meta-analysis

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Population</th>
<th>Studies (n)</th>
<th>Outcome(s)</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
</table>
| Intraperitoneal Cisplatin Vs. Intravenous Cisplatin | Patients with stage III, optimally debulked ovarian cancer (N=1,716) | 6 RCTs | OS, PFS, Toxicity | - The pooled hazard ratio (HR) for PFS of IP cisplatin as compared to IV treatment regimens is 0.792 (95% CI: 0.688–0.912, P =.001), and the pooled HR for OS is 0.799 (95% CI: 0.702–0.910, P =.0007)
- There was a significant increased risk among those treated with IP cisplatin of grade 3 or greater gastrointestinal symptoms (four studies, OR = 1.95, 95% CI: 1.17–3.24, P = .01) and fever (four studies, OR = 1.7, 95% CI: 1.02–2.84, P = .04).
- There was a significant increased risk of ototoxicity those randomized to IV therapy (OR = 0.38, 95% CI: 0.19–0.73, P = 0.004); however, only two studies (SWOG-8501 and UCSD study) provided data for this analysis. | Hess et al, 2007 |
| Intraperitoneal chemotherapy Vs. Intravenous chemotherapy | Patients with newly diagnosed epithelial ovarian cancer that was either stage III or ranged from stage II to stage IV (N=1,806) | 7 RCTs | OS, PFS, Toxicity | - Three large Phase III trials detected statistically significant overall survival benefits with intraperitoneal cisplatin-containing chemotherapy compared with intravenous chemotherapy alone. The improvements in survival were 8 months, 11 months, and 16 months, respectively.
- Pooled analysis from 6 of the 7 randomized trials confirmed the survival effect with intraperitoneal chemotherapy compared with intravenous chemotherapy alone (relative risk, 0.88; 95% confidence interval, 0.81–0.95).
- Severe adverse events and catheter-related complications with intraperitoneal chemotherapy were significantly more common and often were dose-limiting. | Elit et al, 2007 |

### Randomized control trials

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Population</th>
<th>Follow-up</th>
<th>Outcome(s)</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental cisplatin dose-dense arm Vs. Control arm (standard cisplatin treatment)</td>
<td>Patients with histologically confirmed advanced ovarian or fallopian tube cancer, FIGO stage III–IV Median age, 57yrs (n=285)</td>
<td>Median, 16.8yrs</td>
<td>P: PFS S: OS, overall response to chemotherapy and toxicity</td>
<td>- No differences were observed between the two treatments in PFS (experimental arm: 17.2 months; control arm: 18.1 months; HR = 1.08, 95% confidence interval [CI] = 0.83 to 1.40; P = .57) and in OS (experimental arm: 35 months; control arm: 32 months; HR = 0.97, 95% CI = 0.75 to 1.26; P = .97).</td>
<td>Fruscio et al 2011</td>
</tr>
</tbody>
</table>
| Cisplatin + paclitaxel 24-hour infusion (Arm 1) | Patients had histologically confirmed EOC, fallopian tube, or primary peritoneal cancer Median age, 58yrs (n=280) | NR | P: OS S: PFS, CR, toxicity | • In arm 1, 80% of patients completed all six cycles compared with 83% of patients in arm 2.  
• Grade 4 granulocytopenia was more common in arm 1 (79% v 54%; P < .001) whereas grade 3 or worse anemia was more severe in arm 2 (6% v 18%; P < .003).  
• The median progression-free survival was 1.03 years for arm 1 versus 1.05 years for arm 2.  
• The median OS was 2.49 and 2.54 years for arms 1 and 2, respectively.  
• There have been 237 reported deaths. The relative death rate was approximately 12% greater in arm 2 (hazard ratio, 1.12; 95% CI, 0.860 to 1.45) | Spriggs et al 2007 (GOG study) |
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<tbody>
<tr>
<td>Vs. Cisplatin + Paclitaxel 96-Hour Infusion (Arm 2)</td>
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</tbody>
</table>
| Carboplatin + Paclitaxel ×3 cycles | Patients with histological diagnosis of epithelial ovarian cancer Median age, 55.5yrs (n=427) | Median, 6.8 yrs | Recurrence & toxicity | • Grade 3 or 4 neurotoxicity occurred in 4/211 (2%) and 24/212 (11%) treated patients on the 3- and 6-cycle regimens, respectively (p<0.01); 6 cycles also caused significantly more severe anemia and granulocytopenia.  
• The recurrence rate for 6 cycles was 24% lower (hazard ratio [HR]: 0.761; 95% confidence interval [CI]: 0.51–1.13, p<0.18), and the estimated probability of recurrence within 5 years was 20.1% (6 cycles) versus 25.4% (3 cycles).  
• The overall death rate was similar for these regimens (HR: 1.02; 95% CI: 0.662–1.57). | Bell et al 2006 (GOG study) |
| Vs. Carboplatin + Paclitaxel ×6 cycles | | | | | |
| Conventionally dosed chemotherapy (group A) | Patients with histologically confirmed stage III ovarian cancer, presence of a residual tumour mass 2 cm or smaller at the time of surgery Median age, 54yrs (n=42) | Median, 81 months | P: PFS S: OS | • The trial was closed early after 42 patients were entered due to slow accrual.  
• The median progression-free survival time was 15.9 and 16.6 months (hazard ratio, HR 0.83; 95% CI 0.41–1.69, P = 0.61) and the median overall survival time was 43.7 and 64.3 months (HR 0.74; 95% CI 0.34–1.61, P = 0.44) in groups A and B, respectively.  
• Although one patient died of HDCT-related toxicity, the regimen was otherwise relatively well tolerated. | Grennan et al 2006 (FINOVA study) |
| Vs. Conventional dose chemotherapy followed by HDCT (group B) | | | | | |
| Docetaxel alone (arm A) | Patients with histologically confirmed epithelial ovarian carcinoma, fallopian tube cancer or ovarian-type primary peritoneal cancer Median age, NR (n=132) | Median, 30 months | P: Completion rate S: PFS toxicity, QOL | • None of the arms demonstrated an eight cycle completion rate (70.5/72.7/45.5% in arms A/B/C, respectively), which was statistically greater than 60% (P=0.102, P=0.056, P=0.982) which was our formal feasibility criteria, although only the completion rate in arm C was clearly worse than this level.  
• The overall response rate (ORR) after carboplatin was 65.7% in 70 evaluable patients.  
• In evaluable patients, ORRs after docetaxel-based cycles were: arm A 84.0% (21 out of 25); arm B 77.3% (17 out of 22); arm C 69.6% (16 out of 23).  
• Median progression-free survival times were: arm A 15.5 months (95% CI: 10.5–20.6); arm B 18.1 months (95% CI: 15.9–20.3); arm C, 13.7 months (95% CI: 12.8–14.6).  
• Neutropenia was the predominant grade 3–4 haematological toxicity: 77.8/85.7/54.4% in arms A/B/C, respectively.  
• Dyspnoea was markedly increased in both gemicitabine-containing arms (P=0.001) but was worse in arm C | Vasey et al 2006 (SCOTROC 2A trial) (feasibility study) |
| Vs. Docetaxel–Gemcitabine (3-eeekly)(arm B) | | | | | |
| Vs. Docetaxel–Gemcitabine (weekly)(arm C) | | | | | |

**Trials comparing double agent chemotherapy**

| GC | Patients who have had surgery ≤12 weeks before enrollment, histological diagnosis of stage IC, II, III, or IV | NR | P: PFS S: OS | • Patients with complete response (CR) were allowed optional consolidation with paclitaxel 135 mg/m2 every 28 days for 12 months.  
• Patients without CR received single-agent crossover therapy at induction doses/schedules until CR, disease progression (PD), or unacceptable toxicity.  
• 155 patients without CR received single-agent crossover | Gordon et al 2009, 2011 & Teneriello 2010 (abstract) |
<p>| Vs. | | | | | |
| TC | | | | | |</p>
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>Median Age</th>
<th>PFS/OS/RR/HR</th>
<th>Toxicity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel ± Cisplatin (PT) vs. Carboplatin (TC)</td>
<td>Patients with histopathologically confirmed ovarian cancer stages IIB-IV</td>
<td>56yrs (n=798)</td>
<td>NR</td>
<td>P: PFS, S: RR, toxicity, QOL</td>
<td>Previously reported data showed that patients undergoing TC or PT did not differ in PFS and OS. However, the TC arm was superior, indicating a better overall QoL compared with the PT arm. Controlling for toxicity and age, a significant treatment by assessment time interaction was found for four QoL functioning scales and three symptoms scales. Patients in the TC arm showed better means scores after treatment on overall QoL (P = .012), physical functioning (P = .012), role functioning (P = .005), and cognitive functioning (P = .024), compared with the PT arm.</td>
</tr>
<tr>
<td>Docetaxel + Carboplatin vs. Paclitaxel + Carboplatin</td>
<td>Patients with histopathologically confirmed FIGO stages IC-IV ovarian cancer</td>
<td>56.2yrs (n=29)</td>
<td>Median, 30 months</td>
<td>P: PFS, S: OS, toxicity, QOL</td>
<td>The two arms showed similar progression-free survival. Grade 4 neutropenia occurred more frequently in the docetaxel-carcoblatin group (84.6%) than in the paclitaxel-carcoblatin group (43.8%), while sensory neurotoxicity was less frequent in the docetaxel-carcoblatin group (53.8%) than in the paclitaxel-carboplatin (68.8%) group. There were significant differences in the quality-of-life data in favor of docetaxel-carboplatin.</td>
</tr>
<tr>
<td>Carboplatin + Docetaxel vs. Docetaxel + Irinotecan</td>
<td>Patients with histopathologically confirmed EOC, fallopian tube cancer or ovarian-type primary peritoneal carcinoma</td>
<td>56yrs (n=100)</td>
<td>Median, 17.1 months</td>
<td>Completeness rate</td>
<td>Neither arm met the formal feasibility criterion of an eight-cycle treatment completion rate that was statistically greater than 60% (arm A 71% (90% confidence interval (CI) 58–81%; P=0.079; arm B 67% (90% CI 55–78%; P=0.184)). Median-dose intensities were &gt;85% of planned dose for all agents. In arms A and B, 15.6 and 12.2% of patients, respectively, withdrew owing to treatment-related toxicity. Grade 3–4 sensory neurotoxicity was more common in arm A (1.9 vs 0%) and grade 3–4 diarrhoea was more common in arm B (0.6 vs 3.5%). Of patients with radiologically evaluable disease at baseline, 50 and 48% responded to therapy in arms A and B, respectively. Median progression-free survival was 17.1 and 15.9 months, respectively. Although both arms just failed to meet the formal statistical feasibility criteria, the observed completion rates of around 70% were reasonable.</td>
</tr>
<tr>
<td>CT Vs. C + PLD</td>
<td>Patient with a cytologic or histologic diagnosis of epithelial ovarian cancer stage IC to IV, an Eastern Cooperative Oncology Group performance status2</td>
<td>Median age, 57yrs (n=820)</td>
<td>Median, 40 months</td>
<td>P: PFS, S: OS, toxicity, QOL</td>
<td>Occurrence of PFS events substantially slowed before obtaining the planned number. Therefore, in concert with the Independent Data Monitoring Committee, final analysis was performed with 556 events. Median PFS times were 19.0 and 16.8 months with carboplatin/PLD and carboplatin/paclitaxel, respectively (HR, 0.95; 95% CI, 0.81 to 1.13; P=.58). Median overall survival times were 61.6 and 53.2 months with carboplatin/PLD and carboplatin/paclitaxel, respectively (HR, 0.89; 95% CI, 0.72 to 1.12; P=.32). Carboplatin/PLD produced a similar response rate but different toxicity (less neurotoxicity and alopecia but more hematologic adverse effects). There was no relevant difference in global quality of life after three and six cycles.</td>
</tr>
</tbody>
</table>

**Notes:**
- HR = hazard ratio
- CI = confidence interval
- PFS = progression-free survival
- OS = overall survival
- RR = response rate
- QOL = quality of life
- GC = gemcitabine/cisplatin
- SCOTROC = Scottish Ovarian Cancer Trial in Randomised Controlled Trials
- 2A trial = Level 2 evidence, randomized controlled trial
Concerning symptom experience, patients undergoing TC showed less nausea and vomiting ($P < .001$), less appetite loss ($P < .001$), and less fatigue ($P = .033$) after completion of treatment compared with patients undergoing PT.

<table>
<thead>
<tr>
<th>Docetaxel + Cisplatin vs. Docetaxel + Carboplatin</th>
<th>Patients with FIGO stage Ic–IV ovarian cancer Median age, 54yrs (n=50)</th>
<th>NR</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall, 103 cycles of docetaxel–cisplatin treatment and 130 cycles of docetaxel–carboplatin treatment were delivered.</td>
<td>The major toxicity was neutropenia in both regimens. The total incidence of grades 3 and 4 neutropenia was 83% (19/23) in the docetaxel–cisplatin arm and 96% (26/27) in the docetaxel–carboplatin arm. The incidence of grade 4 neutropenia was significantly lower in the docetaxel–cisplatin arm ($39% (9/23)$ versus $74% (20/27)$). Minagawa et al 2006 (feasibility study)</td>
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</table>

<table>
<thead>
<tr>
<th>Cyclophosphamide + Cisplatin vs. Paclitaxel + Cisplatin</th>
<th>Patients with histologically confirmed FIGO stages IIb to IV ovarian cancer Median age, 58 yrs (n=152)</th>
<th>NR</th>
<th>QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance with QOL questionnaire completion was excellent (81% to 93%).</td>
<td>In general, deterioration was seen in the QOL domains immediately after chemotherapy (day 8 of cycle 1), followed by clinically meaningful improvements compared with baseline (change scores ≥ 10) in both arms during the treatment period in a number of domains and items, including global QOL, emotional function, social function, fatigue, pain, sleep, constipation, appetite, abdominal swelling, and abdominal cramps.</td>
<td>Bezjak et al 2004</td>
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</tr>
</tbody>
</table>

**Trials comparing multiple agents**

<table>
<thead>
<tr>
<th>Carboplatin + Paclitaxel vs. Carboplatin + Paclitaxel + Bevacizumab</th>
<th>Women with high-risk early (FIGO stage I or IIa (grade 3 or clear cell), capped 10%) or advanced (stage IIIb-IV) epithelial ovarian, primary peritoneal or fallopian tube cancer Median age, 57 yrs (n=1,528)</th>
<th>Median, 28 months</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>There were 377 deaths (200 standard, 177 bevacizumab), HR=0.84, 95%CI=0.69 to 1.03, $p=0.099$.</td>
<td>Exploratory subgroup analysis of poor prognosis patients: 188 deaths (109 standard, 79 bevacizumab), HR=0.64, 95%CI=0.48 to 0.85, $p=0.0022$ with $p=0.015$ for test for interaction (treatment/risk group). Kristensen et al 2011 (Abstract)</td>
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<table>
<thead>
<tr>
<th>Carboplatin + Paclitaxel (R1) vs. Carboplatin + Paclitaxel + Bevacizumab (R2) vs. Maintenance Bevacizumab (R3)</th>
<th>Patients with ovarian cancer Median age, NR (n=1,693)</th>
<th>NR</th>
<th>QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>At cycle 4, the patients in R2 ($p &lt; 0.001$) and R3 ($p &lt; 0.001$) reported QOL scores that were 2.7 points (98.3% CI: 0.88–4.57; $p &lt; 0.001$; effect size = 0.18) and 3.0 points (98.3% CI: 1.13–4.78; $p &lt; 0.001$; effect size = 2.0) lower respectively, than those in R1.</td>
<td>While the observed differences in QOL were statistically significant, they were not considered clinically significant.</td>
<td>Monk et al 2011 (Abstract)</td>
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<tr>
<td>The difference in QOL scores between R1 and R3 remained statistically significant up to cycle 7, 2.3 points lower (98.3% CI: 0.33–4.14; $p = 0.005$; effect size = 0.15) in group R3. These scores were not statistically different between patients in R2 and R3.</td>
<td>A similar trend was evident in subscale analyses, in which the patients in R2 and R3 reported statistically (not clinically) lower functioning than those in R1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The percentage of patients who reported abdominal discomfort (AD score &gt;0) dropped over time, without significant differences between study arms.</td>
<td>The percentage of patients who reported abdominal discomfort (AD score &gt;0) dropped over time, without significant differences between study arms.</td>
<td>Du Bois et al</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TC</th>
<th>Patients with ovarian cancer Median, P: OS</th>
<th>Grades 3 to 4 hematologic toxicity and fatigue occurred</th>
<th>Du Bois et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Official title</td>
<td>Status</td>
<td>Protocol ID</td>
</tr>
<tr>
<td>-------------</td>
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<td>-------------</td>
</tr>
<tr>
<td>Paclitaxel (IV) wkly + carboplatin IV x3wks</td>
<td>A randomized phase II/III trial of intravenous (iv) paclitaxel weekly plus iv carboplatin once every 3 weeks versus iv paclitaxel weekly plus intraperitoneal (IP) carboplatin once every 3 weeks in women with epithelial ovarian, fallopian tube or primary peritoneal cancer</td>
<td>Recruiting</td>
<td>NCT01506856</td>
</tr>
<tr>
<td>Paclitaxel (IV) wkly + carboplatin (IP) x 3 wks</td>
<td>Paclitaxel + Carboplatin + Sorafenib Vs. Paclitaxel + Carboplatin</td>
<td>A Randomized Phase II Study of Paclitaxel/Carboplatin With or Without Sorafenib in the First-Line Treatment of Patients With Stage III/IV Epithelial Ovarian Cancer</td>
<td>Active</td>
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Abbreviations: G=Gemcitabine; C=Carboplatin; T=Paclitaxel; CPT-P=Irinotecan hydrochloride plus cisplatin; E=Epirubicin; CCC= Clear cell adenocarcinoma of the ovary; EOC = Epithelial ovarian cancer; CR=Complete Response; SCOTROC 2A=Scottish Randomized Trial in Ovarian Cancer 2A; MITO-2=Multicentre Italian Trials in Ovarian Cancer-2; HeCOG = Hellenic Cooperative Oncology Group study; FINOVA = Finnish Ovarian Cancer study; GOG = Gynecologic Oncology Group study; JGOG = Japanese Gynecologic Oncology Group study

**Instructions.** These questions are answered by the Clinical Expert assigned by the DSG/GDG. Beginning at question 1 answer the questions in order.

1. **Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?**
   - **Yes** – In view of mature trial results consistently showing significant benefits of intra peritoneal chemotherapy in optimally debulked patients, recommendation about IP chemo should be revised.
   - **Yes** – The published results of ICON 7 and GOG 218 should be included as they support a significant positive effect for Bevacizumab in combination with Carboplatin Paclitaxel
   - **Yes** – Recent confirmatory result of the JGOG3016 trial (Lancet 2009, 374:1331) was presented at ASCO 2012 showing benefit for a dose dense strategy should be included and remain an option for front line therapy (Abstract No:5003 )

2. **On initial review,**
   - **a. Does the newly identified evidence support the existing recommendations?**
   - **b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?**
   - No to both please see comments above

   Answer Yes or No to each, and explain if necessary:
3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:

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<tr>
<td>Yes</td>
<td>see above</td>
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</table>

4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?

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<tr>
<td>Not Applicable</td>
<td></td>
</tr>
</tbody>
</table>

5. If Q2, Q3, and Q4 were all answered NO, this document should be **ARCHIVED** with no further action.

### New References Identified (alphabetical order):


26. Teneriello MG, Gordon AN, Lim P, Janicek M. Phase III trial of induction gemcitabine (G) or paclitaxel (T) plus carboplatin (C) followed by elective T consolidation in advanced ovarian cancer (OC): Final safety and efficacy report. Journal of Clinical Oncology. 2010;1).


Search strategy:

Embase
1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative syntheses or quantitative overviews).tw.
4. (systematic adj (review$ or overview$)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. 9 or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomis$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinical adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or trip$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. Animal/
33. Human/
34. 32 not 33
35. 31 not 34
36. ovarian neoplasms/
37. ovarian neoplasms?.tw.
38. ovarian cancer.tw.
39. epithelial ovarian cancer.tw.
40. 36 or 37 or 38 or 39
41. antineoplastic agents/
42. drug therapy/
43. chemotherapy.tw.
44. first line chemotherapy.tw.
45. 41 or 42 or 43 or 44
46. 40 and 45
47. 35 and 46
48. (200426$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$).ew.
49. 47 and 48

**Medline**

1. meta-Analysis as topic.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative syntheses or quantitative overview?).tw.
5. (systematic adj (review$ or overview$)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psychnfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. (((singl$ or doubl$ or trebl$ or trip$) adj (blind$3 or mask$3 or dummy))).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. Animal/
38. Human/
39. 37 not 38
40. 36 not 39
OUTCOMES DEFINITION

1. **ARCHIVE** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the phrase “Archived document, not for use in clinical decision making.”

2. **ENDORSEMENT** – An endorsed document is a document that has been reviewed by the DSG for currency and relevance, and the DSG believes it is still useful as guidance for clinical decision making. A document may be endorsed because the DSG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DEFERRAL** – A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action due to a number of reasons. The reasons for deferral should be found in the DART form and on the document.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.