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PRACTICE GUIDELINE

Systemic therapy for recurrent epithelial ovarian cancer: a clinical practice guideline

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ABSTRACT

Objective The purpose of this guideline is to recommend systemic therapy options for women with recurrent epithelial ovarian cancer, including fallopian tube and primary peritoneal cancers.

Methods This document updates the recommendations published in the 2011 *Optimal Chemotherapy for Recurrent Ovarian Cancer* guideline from Cancer Care Ontario. Draft recommendations were formulated based on evidence obtained through a systematic review of phase II and III randomized controlled trials (RCTs). The draft recommendations underwent internal review by clinical and methodology experts, and external review by clinical practitioners through a survey assessing the clinical relevance and overall quality of the guideline. Feedback from the internal and external reviews was integrated into the clinical practice guideline.

Results The primary literature search yielded thirty-six primary research papers representing thirty RCTs that met the eligibility criteria. The guideline provides recommendations for patients with serous tumour histologies and with recurrent, platinum-resistant, and platinum-sensitive ovarian cancer.

Conclusions The body of evidence from trials that included olaparib and bevacizumab consistently shows a benefit in progression-free survival (PFS) without a corresponding benefit in overall survival (OS). The Working Group for this guideline designated PFS, which is associated with symptom control, as a critical outcome. A finding of net benefit can therefore be concluded based on significant differences in PFS. However, that benefit is not without identified harms. Given the identified harms, patient involvement in the decision-making process must take into consideration the side effect profiles of olaparib and bevacizumab within the context of improved PFS but minimal change in OS.

Key Words Cancer Care Ontario, recurrent epithelial ovarian cancer, systemic therapy, guideline recommendations

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INTRODUCTION

In Canada, ovarian cancer is the 5th leading cause of cancer death among women and the leading cause of gynecologic cancer mortality. New cases of ovarian cancer were estimated to reach 2800 in Canada in 2015[1]. Ovarian cancer is usually diagnosed at an advanced stage, and most patients experience relapse after primary therapy, resulting in a survival rate of approximately 10%–30%[2].

One of the most frequently documented predictors of response to chemotherapy in women with recurrent ovarian cancer is the platinum-free interval, defined as the period of time from the last dose of platinum-based therapy until disease progression[3]. However, some patients become increasingly resistant to platinum-based therapies over time, and some women respond to multiple lines of treatment. Although responsiveness to platinum-based therapies would be more accurately viewed as occurring on a continuum[4], the platinum sensitivity of patients is, for the purposes of treatment planning and research, often stratified as follows[5]:

- *Platinum-sensitive patients*
  Patients with a platinum-free interval of 6 months or longer (that is, patients with disease that relapses 6 or more months after completion of initial therapy)
- *Platinum-resistant patients*
  Patients with a platinum-free interval of less than 6 months (that is, patients whose disease relapses less than 6 months after completion of initial therapy)

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- *Platinum-refractory patients*
  Patients whose disease progressed during previous platinum-containing therapy

Many patients with recurrent ovarian cancer do not survive their cancers, and as a result, the duration of survival (prolonged PFS) and quality of life (QOL) are important outcomes. In this population, PFS is therefore a valid study endpoint. With those principles in mind, the Working Group chose PFS as one of the primary outcomes of interest.

RESEARCH QUESTION

What is the optimal systemic therapy for women with recurrent ovarian cancer who have previously received platinum-based chemotherapy?

These study comparisons were considered: any systemic therapy option compared with another systemic therapy option, and any systemic therapy option compared with placebo.

TARGET POPULATION

The target population consists of women with recurrent epithelial ovarian cancer who have previously received platinum-based chemotherapy. Specific subgroups of interest in the target population are identified based on their response to therapy.

INTENDED USERS

The intended users of this guideline are gynecologic oncologists or medical oncologists in the province of Ontario.

DEVELOPMENT OF RECOMMENDATIONS

The Program in Evidence-Based Care (PEBC) at Cancer Care Ontario (CCO) produces evidence-based and evidence-informed guidance documents using the methods of the practice guidelines development cycle[6,7]. The process includes a systematic review, interpretation of the evidence by the Working Group, draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The project was led by a small Working Group consisting of members of the Gynecologic Cancer Disease Site Group. The Working Group was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group members had expertise in gynecologic oncology, medical oncology, and health research methodology.

INTERNAL AND EXTERNAL REVIEW

Before submission of the draft report for external review, the systematic review and the guideline recommendations were reviewed by the PEBC's Report Approval Panel, which consists of 2 members, one of whom is an oncologist with expertise in clinical and methodology issues. The PEBC's Report Approval Panel reviewed the draft systematic review and the updated guideline and provided feedback.

The external review by clinical practitioners used two processes: a targeted peer review, and a professional consultation.

In the targeted peer review, 4 reviewers from Ontario (considered to be clinical or methodology experts on the topic) agreed to participate. They reviewed a draft report and answered a questionnaire evaluating the methods, results, and interpretive summary used to inform the draft recommendations.

In the professional consultation, feedback was obtained through a brief online survey of medical and gynecologic oncologists who treat ovarian cancer in Ontario.

The draft systematic review of guidelines and the updated guideline recommendations were distributed to health care providers in the province of Ontario. Results of those sources of feedback can be found in the full guideline report on the CCO Web site: https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/gynecologic_cancer/.

LITERATURE SEARCH RESULTS

In 2011, CCO's PEBC published a similar guideline titled *Optimal Chemotherapy for Recurrent Ovarian Cancer*[8]. The present updated guideline incorporates new evidence reported since the previous guideline was published. Where new evidence did not alter the original recommendations, the 2011 recommendations are endorsed. Where new evidence altered the original recommendations, the 2011 recommendations are appropriately modified. *De novo* recommendations were formulated when new evidence was available to inform new original recommendations.

Search for Existing Guidelines, Systematic Reviews, and Primary Literature

A search of the MEDLINE and EMBASE databases and the Cochrane Database of Systematic Reviews for systematic reviews and primary studies was conducted from 1 April 2011 to 30 May 2017.

Study Selection Criteria and Process

Included studies are those that examined systematic therapy for women with epithelial ovarian, primary peritoneal, and fallopian tube cancers, collectively called "epithelial ovarian cancers"[5], who fell into any of the 3 platinum categories outlined in the Introduction. Phase II or III RCTs published in English that compared one systemic therapy option with another systemic therapy option or with a placebo were included. No minimum sample size was specified. The systematic review of the evidence focuses on systemic therapy and excludes intraperitoneal chemotherapy, hormonal therapy, or chemotherapy with bone marrow or stem-cell transplantation. A review of the titles and abstracts that resulted from the literature search was conducted by Erin Kennedy, Jennifer Salerno, and author NC. The remaining authors reviewed the articles considered for inclusion and agreed on the full-text articles to be included.

Data Extraction and Assessment of Study Quality

Data were extracted by Erin Kennedy, Jennifer Salerno, and author NC and were audited by a project research assistant. The data elements were population, intervention, and outcomes information. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) process was used to assess the quality of included studies with respect to the critical and important outcomes[9]; however, given the complexity and heterogeneity of the study designs and comparisons, GRADE was used as an overall critical appraisal guide. In addition, because of the heterogeneity of protocols, populations, and interventions in the included studies, a meta-analysis was not considered.

Search for Existing Guidelines

A search for existing guidelines was undertaken to determine whether an existing guideline could be adapted or endorsed. *A priori,* the Working Group recognized the prior version of the guideline developed by the Gynecologic Cancer Disease Site Group and published by the PEBC[8]. Nine guidelines were identified. The Working Group felt that none of those guidelines were suitable for adaptation or endorsement because the guideline recommendations did not align with the Working Group's research question and methods.

Search for Existing Systematic Reviews and Primary Literature

No systematic reviews that met the inclusion criteria were identified. The reviews that were located were judged unsuitable because they were too old, could not be obtained, had inclusion criteria different from those defined for the present guideline, or included first-line treatments in their analysis.

The primary literature search yielded thirty-six primary research papers representing thirty phase II or III RCTs that met the eligibility criteria[10–45]. Phase III studies that were of high quality and had a low risk of bias received more weight in determining the guideline recommendations presented here.

Six of the included studies were assessments of olaparib in populations of women with serous tumour histologies[12,22,25,26,29,37]. Five studies considered systemic treatment in patients with recurrent ovarian cancer[16,21,32,33,35]. Seven studies addressed systemic treatment in a platinum-sensitive population[10,11,15,23,31,41,44]. Twelve studies reported on patients with platinum-resistant ovarian cancer[14,17–19,24,30,36,38–40,43,45].

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF THE EVIDENCE

Recommendations 1, 2, and 3 are endorsements of recommendations found in the 2011 version of the guideline; the original recommendations continue to be valid and have not changed.

Recommendations 4 and 5 are new in this version of the guideline.

Recommendation 1

Systemic therapy for recurrent ovarian cancer is not curative. As such, it is recognized that, to determine the optimal therapy, each patient has to be assessed individually in terms of recurrence, sensitivity to platinum, toxicity, ease of administration, and patient preference.

Recommendation 2

All patients should be offered the opportunity to participate in clinical trials, if appropriate.

Recommendation 3

With respect to chemotherapy for patients with platinum-sensitive recurrent ovarian cancer,

- if the option to participate in a clinical trial is not available, combination platinum-based chemotherapy should be considered, providing that there are no contraindications. The decision about which combination to use should be based on toxicity experienced with primary therapy, patient preference, and other factors. Recommended combinations are
  - carboplatin and paclitaxel (C-P).
  - carboplatin and gemcitabine.
  - carboplatin and pegylated liposomal doxorubicin (C-PLD).
- if combination platinum-based chemotherapy is contraindicated, then a single platinum agent should be considered. Carboplatin has demonstrated efficacy in multiple trials and has a manageable toxicity profile.
- if a single platinum agent is not being considered (for example, because of toxicity or allergy), then monotherapy with paclitaxel, topotecan, or pegylated liposomal doxorubicin is a reasonable treatment option.

Key Evidence for Recommendation 3

A 976-patient study, CALYPSO[46], compared C-P with C-PLD and found an improvement in PFS with the C-PLD combination (11.4 months vs. 9.3 months, $p = 0.005$), a more favourable toxicity profile, no difference in OS (although significantly more patients crossed over to the C-PLD arm), and a superior crossover treatment rate in the C-P arm. Global QOL scores did not differ between the groups[47].

A 672-patient study, OVA-301[48], compared PLD with trabectedin–PLD, and found a statistically significantly improved PFS with the combination therapy (7.3 months vs. 5.8 months, $p = 0.019$). Despite that finding, which implies the viability of the combination as a treatment option, the trabectedin–PLD combination is not recommended at this time, based on the findings of no difference in QOL[49] or OS[50], the lack of clinical significance of a 6-week PFS difference, the lack of comparison with the Gynecologic Cancer Intergroup standard of a taxane and a platinum agent[3], and the elevated rate, in the combination group, of adverse events such as raised liver enzymes, nonfatal congestive heart failure, and neutropenia.

A study by Sehouli *et al.*[51] of topotecan compared with topotecan combined with other agents did not find a benefit with the combination therapy in a population of mainly platinum-sensitive women; thus, topotecan combination therapy is not recommended.

Two smaller trials that compared PLD with gemcitabine showed no difference in PFS. A small significant difference

in OS was found in one trial (56 weeks for PLD vs. 51 weeks for gemcitabine, $p = 0.048$)[52]. The adverse events profiles for the two agents differ, and therefore gemcitabine can be considered to be another option in this patient population, considering patient preference and previous toxicity[52,53].

Recommendation 4

Women with platinum-sensitive recurrent ovarian cancer should, after a discussion about the safety profile, be offered chemotherapy with biologics.

These targeted agents can be considered:

- Bevacizumab combined with combination chemotherapy and as maintenance therapy
- Cediranib administered during the chemotherapy and as maintenance therapy
- For patients with known *BRCA1* or *BRCA2* mutations (somatic and germline), polyADP–ribose polymerase (PARP) inhibitors are recommended as maintenance treatment after platinum-based chemotherapy for recurrent disease
- For patients who are *BRCA* wild-type, niraparib can be considered as maintenance after platinum-based chemotherapy for recurrent disease.

Qualifying Statements for Recommendation 4

With the increase in evidence supporting the use of PARP inhibitors in patients with homologous recombination deficiency mutations, consideration should be given to testing the *BRCA* status of all women with ovarian cancer at initial diagnosis.

The PARP inhibitors have been associated with an increase in PFS in patients with *BRCA* mutations, but without a significant improvement in OS.

In women with wild-type *BRCA,* PARP inhibitors have also been associated with a minor improvement in PFS.

Key Evidence for Recommendation 4

In the platinum-sensitive population of the OCEANS phase III RCT, the PFS for bevacizumab plus gemcitabine and carboplatin (BEV+CT) was shown to be superior compared with carboplatin plus gemcitabine plus placebo (CT) [hazard ratio (HR): 0.48; 95% confidence interval (CI): 0.39 to 0.61]. The median PFS was 12.4 months in the BEV+CT arm compared with 8.4 months in the CT arm[10].

In the platinum-sensitive population of the moderate-quality ICON6 phase III RCT, the PFS for arm C with cediranib was shown to be superior compared with the reference arm A of platinum-based therapy plus placebo (HR: 0.56; 95% CI: 0.44 to 0.72). Median PFS was 11.0 months in the experimental arm and 8.7 months in the nonexperimental arm[11].

Compared with placebo, niraparib was associated with a significantly prolonged PFS in platinum-sensitive patients with no germline *BRCA* mutations (HR: 0.45; 95% CI: 0.34 to 0.61; $p < 0.001$)[12].

Interpretation of the Evidence for Recommendation 4

The listed recommendations are conditional in nature (that is, "can be considered") given the trade-off between the benefit (that is, PFS) weighed against the harms (that is, adverse effects).

Based on moderate-quality evidence in the OCEANS trial[10,13], statistically significantly increased risks for BEV+CT compared with CT were shown for these adverse events:

- Any serious adverse event (grades 3–5): relative risk (RR), 1.53; 95% CI, 1.11 to 2.09
- Grade 3 or greater hypertension: RR, 21.22; 95% CI, 5.21 to 86.51
- Grade 3 or greater proteinuria: RR, 12.73; 95% CI, 3.06 to 52.96

Notably, the confidence intervals for grade 3 or greater hypertension and proteinuria were very wide because of the few events (<5) occurring in the CT arm.

In the ICON6 trial[11], statistically significantly increased risks during the chemotherapy phase for the combined arms B and C of platinum-based chemotherapy (CT) plus cediranib compared with reference arm A of CT plus placebo were shown for these adverse events:

- Grade 3 or greater fatigue: RR, 2.11; 95% CI, 1.07 to 4.11
- Grades 3–4 diarrhea: RR, 5.94; 95% CI, 1.45 to 24.34
- Grades 3–5 hypertension: RR, 3.32; 95% CI, 1.21 to 9.10

Notably, the confidence intervals for grades 3–5 diarrhea were very wide because of the few events (<5) in the reference CT-only arm.

Recommendation 5

With respect to patients having platinum-refractory or platinum-resistant recurrent ovarian cancer,

- lower levels of response to treatment are expected for this group; the goals of treatment should therefore be to improve the patient's QOL by extending the symptom-free interval, reducing symptom intensity, increasing PFS, and if possible, prolonging life.
- monotherapy with a non-platinum agent should be considered given that no advantage appears to accrue to the use of non-platinum-containing combination chemotherapy in this group of patients. Single-agent paclitaxel, topotecan, PLD, and gemcitabine have demonstrated activity in this patient population and are reasonable treatment options.
- there is no evidence to support or refute the use of more than one line of chemotherapy in patients with platinum-refractory or platinum-resistant recurrences. Many treatment options have shown modest response rates, but their benefit over best supportive care has not been studied in clinical trials.
- bevacizumab combined with chemotherapy (PLD, weekly paclitaxel, or topotecan) can be considered for women who meet the eligibility criteria of the AURELIA phase III RCT (confirmed epithelial ovarian, fallopian tube, or primary peritoneal cancer that has progressed within 6 months of completion of 4 or more cycles of platinum-based therapy; age 18 years or greater; Eastern Cooperative Oncology Group performance status of 2 or less; and adequate liver, renal, and bone marrow function). Ineligible patients include those who

have received more than 2 prior anticancer regimens or who have refractory disease; who have a history of bowel obstruction (including subocclusive disease) related to underlying disease; who have a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess; who have evidence of rectosigmoid involvement by pelvic examination, bowel involvement on computed tomography, or clinical symptoms of bowel obstruction.

Qualifying Statements for Recommendation 5

At the time this guideline was written, numerous targeted agents (in addition to vascular endothelial growth factor inhibitors, PD-1 and PD-L1 inhibitors, and other immunotherapies) were under investigation and showing promise in early trials. It is likely that one or more of those agents will become part of the lexicon of treatment protocols in the near future, either independently or in combination with conventional chemotherapy.

Key Evidence for Recommendation 5

Based on moderate-quality evidence in the AURELIA phase III RCT, the HR for PFS in women with platinum-resistant recurrent ovarian cancer was 0.48 (95% CI: 0.38 to 0.60) for chemotherapy including PLD, weekly paclitaxel, or topotecan with bevacizumab (BEV+CT) compared with the same regimen without bevacizumab (CT). Median PFS was 6.7 months in the BEV+CT arm compared with 3.4 months in the CT arm[14].

Statistically significantly increased risks for BEV+CT compared with CT were shown for these adverse events:

- Grade 2 or greater adverse events, including hypertension, gastrointestinal perforation, and fistula or abscess: RR, 3.71; 95% CI, 2.03 to 6.78[14]
- Grade 3 or greater adverse events including hypertension, proteinuria, gastrointestinal perforation, bleeding, thromboembolic event, wound healing, reversible posterior leucoencephalopathy syndrome, congestive heart failure, and cardiac disorders: RR, 2.64; 95% CI, 1.44 to 4.84[14]

Based on very low-quality evidence, statistically significant improvements of 15% or more in abdominal or gastrointestinal symptoms were shown for BEV+CT compared with CT (RR: 2.33; 95% CI: 1.37 to 3.97)[14].

Interpretation of the Evidence for Recommendation 5

Based on moderate-quality evidence, a beneficial effect on PFS was associated with BEV+CT.

The listed recommendation is conditional in nature (that is, "can be considered") because of the detection of adverse events with the use of BEV+CT. Although based on low-quality evidence, the Gynecologic Cancer Disease Site Group accepts lower-tier evidence informing harms outcomes, thereby tempering the recommendation despite evidence for improved PFS.

Further Qualifying Statements

In several trials, PARP inhibitors have been associated with a significant improvement in PFS, although the phase III data in this drug class are limited. Based on current evidence, a conditional recommendation was made for PARP inhibitors in the patient population positive for *BRCA* mutation or homologous recombination deficiency and in the non-*BRCA* population. Olaparib has been approved by the U.S. Food and Drug Administration for recurrent ovarian cancer with germline mutations.

There is increasing evidence to support the unique nature of the numerous histologic subtypes within ovarian cancer. As evidence increases, treatment regimens will be optimized by subtype. Those issues will be addressed in a PEBC guideline currently under development.

IMPLEMENTATION CONSIDERATIONS

In June 2015, cediranib as monotherapy was withdrawn by AstraZeneca from consideration by the European Medicines Agency's Committee for Medicinal Products for Human Use. However, that decision does not affect cediranib as a combination treatment with other agents.

The Gynecologic Cancer Disease Site Group believes that patient preference should play a significant role in disease management in the setting of recurrent ovarian cancer. Because cure is seldom an endpoint in this circumstance, the attitude of the patient with respect to the risks and benefits of chemotherapy compared with palliation are relevant.

Currently, all women with high-grade serous ovarian cancer should be offered testing for *BRCA1* and *BRCA2*. This germline testing has implications for timely access to genetic counselling services and lab results. The impending move to somatic testing will have implications for the funding of the pathology services that will test tissue. It is highly likely that other ovarian histologies will be candidates for testing in the future.

REVIEW AND UPDATE

Guidelines developed by the PEBC are regularly reviewed and updated. Please visit the CCO Web site (http://www.cancercare.on.ca) for the full evidence-based series report and subsequent updates.

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The full recommendation report can be found on the CCO Web site, at the Gynecologic Cancer projects page: https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/gynecologic_cancer/.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: LE's institution receives funding from AstraZeneca for

a trial in which she is co-investigator. The remaining authors have no conflicts to disclose.

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