cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

**Evidence-based Series 4-3 Version 3**

# Optimal Chemotherapy for Recurrent Ovarian Cancer

*M. Fung Kee Fung, E. Kennedy, J. Francis, H. Mackay,*
*and members of the Gynecologic Cancer Disease Site Group*

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

**Report Date: November 21, 2011**

**The full Evidence-based Series (EBS) 4-3 Version 3 is comprised of 4 sections and is available on the CCO Web site (http://www.cancercare.on.ca)**
**PEBC Gynecology Cancer DSG page at:**
**http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/gyn-ebs/**

**Section 1: Guideline Recommendations**
**Section 2A: Version 3 Systematic Review (2011)**
**Section 2B: Version 2 Systematic Review (2006)**
**Section 3: Guideline Development Methods and External Review Process**

For further information about this series, please contact:

**Dr. Michael Fung Kee Fung**, Chair, Gynecologic Cancer Disease Site Group
Ottawa General Hospital, 501 Smyth Road, Ottawa, ON
Phone: 613-737-8560 Fax: 613-737-8828

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/
or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

**Journal Citation (Vancouver Style):**
- Murphy J, Kennedy EB, Dunn S, McLachlin CM, Fung Kee Fung M, Gzik D, et al. Cervical screening: a guideline for clinical practice in Ontario. J Obstet Gynaecol Can. 2012 May;34(5):453–458.
- Murphy J, Kennedy EB, Dunn S, McLachlin CM, Fung Kee Fung M, Gzik D, et al. HPV testing in primary cervical screening: a systematic review and meta-analysis. J Obstet Gynaecol Can. 2012 May;34(5):443–452.

**Guideline Citation (Vancouver Style):** Fung Kee Fung M, Kennedy E, Francis J, Mackay H, and members of the Gynecologic Cancer Disease Site Group. Optimal chemotherapy for recurrent ovarian cancer. Toronto (ON): Cancer Care Ontario; 2011 Nov 21. Program in Evidence-based Care Evidence-Based Series No.: 4-3 Version 3.

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

**Evidence-based Series 4-3 Version 3: Section 1**

# Optimal Chemotherapy for Recurrent Ovarian Cancer: Guideline Recommendations

*M. Fung Kee Fung, E. Kennedy, J. Francis, H. Mackay,*
*and members of the Gynecologic Cancer Disease Site Group*

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

**This Evidence-based Series (EBS) report updates an earlier version completed in 2006.**
**Section 2A contains a systematic review of the relevant evidence from April 2006 to March 2011.**
**Section 2B contains a systematic review of the original evidence up to March 2006.**

**Report Date: November 21, 2011**

## QUESTION

What is the optimal chemotherapy treatment for women with recurrent ovarian cancer who have previously received platinum-based chemotherapy? Outcomes of interest include progression-free survival (PFS), overall survival (OS), adverse events and/or quality of life (QOL), and tumour response rates.

## TARGET POPULATION

The target population comprises women with recurrent epithelial ovarian cancer who have previously received platinum-based chemotherapy. According to a consensus statement developed by the Gynecologic Cancer InterGroup (GCIG), the distinct patient populations in need of specific therapeutic approaches can be defined by the interval from last date of platinum therapy to progression, as measured by serum marker CA-125 and radiological and/or symptomatic criteria. Specific categories have been defined as follows (1):

1. Progression while receiving last line of platinum-based therapy or within four weeks of last platinum dose.
2. Progression-free interval since last line of platinum of less than six months.
3. Progression-free interval since last line of platinum of six to 12 months.
4. Progression-free interval since last line of platinum of more than 12 months.

The first two categories can be labelled platinum-refractory and platinum-resistant, respectively, and for the purposes of making recommendations, they have been combined. The latter two categories comprise the platinum-sensitive population and have also been combined in the recommendations.

**INTENDED USERS**

This guideline is intended for clinicians involved in the delivery of chemotherapy for recurrent ovarian cancer patients.

**RECOMMENDATIONS**

On the basis of the available data from Phase III randomized controlled trials, combined with expert opinion, the Gynecologic Cancer Disease Site Group recommends that:

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

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

- For patients with prior sensitivity to platinum-containing chemotherapy:
  - All suitable patients should be offered the opportunity to participate in randomized controlled clinical trials (RCTs), if appropriate.
  - If the option to participate in an RCT is not available, combination platinum-based chemotherapy should be considered, providing that there are no contra-indications. The decision regarding which combination to use should be based on the considerations listed in the first bullet point above, including 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 across trials and has a manageable toxicity profile.
  - If a single platinum agent is not being considered (e.g., because of toxicity), then monotherapy with paclitaxel, topotecan, or pegylated liposomal doxorubicin is a reasonable treatment option.

- For patients with platinum-refractory or platinum-resistant disease:
  - Lower levels of response to treatment are expected for this group; therefore, the goals of treatment should be to improve QOL by extending the symptom-free interval, reducing symptom intensity, increasing progression free interval, or if possible, prolonging life.
  - All suitable patients should be offered the opportunity to participate in clinical trials, if appropriate.
  - Monotherapy with a non-platinum agent should be considered since there does not appear to be an advantage in the use of non-platinum-containing combination

chemotherapy in this group of patients. Single-agent paclitaxel, topotecan, pegylated liposomal doxorubicin, 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. There are many treatment options that have shown modest response rates but their benefit over best supportive care has not been studied in clinical trials.

**Modifications from 2006 Recommendations**

The recommendations listed above are predominantly unchanged from the 2006 version of this guideline, with the exception of the addition of C-PLD as a treatment option for platinum-sensitive recurrent ovarian cancer, the addition of single-agent gemcitabine as a treatment option for platinum-resistant ovarian cancer, and the clarification of the recommendation for participation in clinical trials.

**KEY EVIDENCE**

In patients with platinum-sensitive ovarian cancer:

- A 976 patient study, CALYPSO (2), compared C-P to C-PLD and found an improvement in PFS with the PLD combination (11.4 versus [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 groups (3).

In a mix of platinum-sensitive and platinum-resistant patients:

- A 672 patient study, OVA-301 (4), compared PLD to trabectedin-PLD, and found a statistically significantly improved PFS with the combination (7.3 vs. 5.8 months, p=0.019). Despite this 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 finding of no differences in QOL (5) or OS (6), the lack of clinical significance of a six-week PFS difference, the lack of comparison with the GCIG standard taxane and platinum agent (1), and the elevated rate of adverse events such as raised liver enzymes, non-fatal congestive heart failure, and neutropenia in the combination group.
- A study by Sehouli et al. (7) of topotecan versus 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) (8). The adverse events profiles differ for these two agents; therefore, gemcitabine can be considered another option in this patient population, considering patient preference and previous toxicity (8,9).

Evidence for all other recommendations can be found in the 2006 version of this guideline, *Optimal Chemotherapy for Recurrent Ovarian Cancer, A Systematic Review* (10), and in Section 2B of this report.

**Qualifying Statements**

The results presented in an abstract from *A Study of Carboplatin and Gemcitabine Plus Bevacizumab in Patients With Ovary, Peritoneal, or Fallopian Tube Carcinoma (OCEANS)*

(11), a randomized, 484-person, double-blinded, placebo-controlled phase III trial of carboplatin and gemcitabine with or without bevacizumab (Bev) in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer showed a significantly longer PFS in the Bev arm (8.4 months vs. 12.4 months, $p<0.0001$). While no recommendation for this treatment option is being made at this time, the publication of the full results of this trial is anticipated and may inform future guideline recommendations.

A recommendation for trabectedin-PLD (4) for carboplatin and cisplatin allergic patients may be reasonable, however because the PFS benefit with this combination was modest, and there was no OS difference, a recommendation for this combination is not being made at this time.

**FUTURE RESEARCH**

The National Institute for Health and Clinical Excellence (U.K.) has plans to update its *Technology Appraisal Guidance No 91: Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for the treatment of advanced ovarian cancer (for relapsed disease only)* (12). The review has been deferred until November 2012 in order to incorporate results from research that is presently ongoing (13), including results from CALYPSO (2) and from studies of trabectedin and gemcitabine.

Three protocols for upcoming reviews were found in the search of the Cochrane Database of Systematic Reviews (Table 6, Section 2).

Increasingly, it is recognized that ovarian cancer histologic subtypes, such as low grade serous cancer, mucinous carcinoma, or clear cell carcinoma should be treated as distinct disease entities with different recommended treatment options. Trials to date have not included these specific groups, so the Working Group is not in a position to make subtype specific recommendations at this time, but as evidence becomes available, it will be incorporated into newer versions of this guideline.

**RELATED GUIDELINES**

- PEBC EBS 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 Report.*

*Funding*

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

*Copyright*

This report is copyrighted by Cancer Care Ontario; the report and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

*Disclaimer*

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

*Contact Information*

For further information about this series, please contact
**Dr. Michael Fung Kee Fung**, Chair, Gynecologic Cancer Disease Site Group
Ottawa General Hospital, 501 Smyth Road, Ottawa, ON
Phone: 613-737-8560 Fax: 613-737-8828

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

## REFERENCES


1. Stuart GCE, Kitchener H, Bacon M, duBois A, Friedlander M, Ledermann J, et al. 2010 Gynecologic Cancer InterGroup (GCIG) consensus statement on clinical trials in ovarian cancer: report from the Fourth Ovarian Cancer Consensus Conference. Int J Gynecol Cancer. 2011;21(4):750-5. doi: 10.1097/IGC.0b013e31821b2568.
2. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, Gebski V, Heywood M, Vasey PA, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol. 2010;28 (20):3323-9.
3. Marth C, Alexandre J, Hanker LC, Brown C, Kaern J, Heywood M, et al. Pegylated liposomal doxorubicin and carboplatin (C-PLD) versus paclitaxel and carboplatin (C-P) in platinum-sensitive ovarian cancer (OC) patients (pts): treatment at recurrence and overall survival (OS) final analysis from CALYPSO phase III GCIG trial. J Clin Oncol. 2011;29 Suppl:abstr 5052.
4. Monk BJ, Herzog TJ, Kaye SB, Krasner CN, Vermorken JB, Muggia FM, et al. Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. J Clin Oncol. 2010;28(19):3107-14.
5. Krasner CN, Poveda A, Herzog T, Vermorken J, Monk B, Zintl P, et al. Health-related quality of life/patient-reported outcomes in relapsed ovarian cancer: Results from a randomized phase III study of trabectedin with pegylated liposomal doxorubicin (PLD) versus PLD alone. J Clin Oncol.. 2009;27 Suppl:abstr 5526.
6. Monk BJ, Herzog TJ, Kaye SB, Krasner CN, Vermorken JB, Muggia F, et al. Final survival results of the randomized phase III study of trabectedin with pegylated liposomal doxorubicin (PLD) versus PLD in recurrent ovarian cancer. J Clin Oncol. 2011;29 Suppl: abstr 5046.
7. Sehouli J, Sommer H, Klare P, Stauch M, Zeimet A, Paulenz A, et al. A randomized multicenter phase III trial of topotecan monotherapy versus topotecan + etoposide versus topotecan + gemcitabine for second-line treatment of recurrent ovarian cancer. Update: full text published in 2008. J Clin Oncol. 2006;24 Suppl 18:abstr 5030.
8. Ferrandina G, Ludovisi M, Lorusso D, Pignata S, Breda E, Savarese A, et al. Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. J Clin Oncol. 2008;26(6):890-6.
9. Mutch DG, Orlando M, Goss T, Teneriello MG, Gordon AN, McMeekin SD, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol. 2007;25 (19):2811-8.
10. Fung Kee Fung M, Oliver T, Elit L, Hirte H, Rosen B, and members of the Gynecology Cancer Disease Site Group. Optimal chemotherapy treatment for women with recurrent ovarian cancer. Toronto (ON): Cancer Care Ontario; 2006 Nov 3. Program in Evidence-based Care Evidence-based Series No.: 4-3 Version 2.2006.
11. Aghajanian C, Finkler NJ, Rutherford T, Teneriello MG, Yi J, Parmar H, et al. OCEANS: A randomized, double-blinded, placebo-controlled phase III trial of chemotherapy with or without bevacizumab (BEV) in patients with platinum-sensitive recurrent epithelial ovarian (EOC), primary peritoneal (PPC), or fallopian tube cancer (FTC). J Clin Oncol. 2011;29 Suppl:abstr LBA5007.
12. National Institute for Health and Clinical Excellence. Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for the treatment of advanced ovarian cancer (for relapsed disease only). London: National Institute for Health and Clinical Excellence (NICE); 2005 May. Technology Appraisal Guidance No.: 91.

13. National Institute for Health and Clinical Excellence. Final appraisal determination: Trabectedin for the treatment of relapsed ovarian cancer [Internet]. London: National Institute for Health and Clinical Excellence (NICE); 2011 [cited 2011 May 16]. Available from: http://guidance.nice.org.uk/TA/Wave19/47/FAD/FinalAppraisalDetermination/pdf/English.