



Evidence-Based Series 4-20 Version 2 IN REVIEW

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

**Systemic Therapy for Recurrent, Metastatic, or
Persistent Cervical Cancer**

*H. Hirte, E.B. Kennedy, M. Fung-Kee-Fung, L. Elit,
and the Gynecologic Cancer Disease Site Group*

Report Date: November 24, 2014

An assessment conducted in November 2020 placed Evidence-based Series (EBS) 4-20 Version 2 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#))

EBS 4-20 Version 2 is comprised of 3 sections. You can access the summary and full report here:

<https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/516>

Section 1:	Guideline Recommendations
Section 2:	Evidentiary Base
Section 3:	Development Methods, Recommendations Development, and External Review Process

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version July 5, 2006	1966-2006	Full Report	Web Publication	N/A
Version 2, November 24, 2014	2006-2014	Full Report	Updated Web Publication	Update of 2006 Recommendations



Evidence-Based Series 4-20 Version 2: Section 1

**A Quality Initiative of the Program in Evidence-based Care (PEBC),
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**Systemic Therapy for Recurrent, Metastatic, or
Persistent Cervical Cancer:
Guideline Recommendations**

*H. Hirte, E.B. Kennedy, M. Fung-Kee-Fung, L. Elit,
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GUIDELINE OBJECTIVES

The objective of this guideline is to update a previous guideline on chemotherapy options for women with recurrent, metastatic, or persistent cervical cancer. The primary outcomes of interest are overall survival rate and quality of life. Other outcomes of interest include response rate, progression-free survival rate, and adverse effects. Second-line or higher therapy options are outside the scope of this guideline.

TARGET POPULATION

These recommendations apply to women with metastatic, recurrent, or persistent cervical cancer for whom systemic therapy is indicated. This includes women with squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix.

INTENDED USERS

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

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

RECOMMENDATION 1

It is recommended that all patients with recurrent, metastatic or persistent cervical cancer be offered the opportunity to participate in randomized clinical trials, if available, that evaluate the efficacy of and adverse effects of systemic therapy regimens.

Summary of Key Evidence and Justification for Recommendation 1

This recommendation is the opinion of the Working Group and was adopted from the previous version of this guideline.

RECOMMENDATION 2

Cisplatin with paclitaxel is recommended for this patient population, and cisplatin in other combinations, including cisplatin-vinorelbine, cisplatin-gemcitabine, and cisplatin-topotecan may also be considered. The substitution of carboplatin for cisplatin in these combinations is also recommended for this target population because carboplatin is associated with fewer adverse effects and greater ease of administration. The selection of combination chemotherapy will depend on toxicity profile, patient preference, and other factors; for example, cisplatin combinations may be preferred in cases of allergic reaction or of difficulty with bone marrow suppression.

Summary of Key Evidence and Justification for Recommendation 2

GOG-0204 [2] which included patients with a performance status ≤ 1 (meaning that they were restricted in physically strenuous activities but ambulatory) [3], compared the combinations cisplatin-vinorelbine, cisplatin-gemcitabine, and cisplatin-topotecan with the reference arm cisplatin-paclitaxel, with OS as the primary endpoint. This study was terminated early because the comparator groups were unlikely to demonstrate any of the combinations statistically superior to the reference arm, thus justifying the recommendation that each of these combinations could be considered options for the target population.

Paclitaxel (175 mg/m² of body surface area for 3 hours on day 1 [3h d1]) in combination with carboplatin (area under the curve [AUC]₀₋₆ 1h d1) has been tested as an alternative to the standard, but more toxic, paclitaxel (135 mg/m² 24h d1) and cisplatin (50 mg/m² 2h d2) in a Japan Clinical Oncology Group phase III noninferiority trial in stage IVB, persistent, or recurrent cervical cancer (JCOG-0505) [1]. This study, published as an abstract, followed 253 patients for 17.4 months and demonstrated the noninferiority of carboplatin-paclitaxel compared with cisplatin-paclitaxel (overall survival rate [OS] 17.5 versus 18.3 months; hazard ratio [HR], 0.99; adjusted 90% confidence interval [CI], 0.79 to 1.25; noninferiority p=0.032). Lower rates of neutropenia, febrile neutropenia, creatinine levels, and early treatment discontinuation due to adverse effects were experienced by patients in the carboplatin combination group, as well as higher rates of thrombocytopenia and neuropathy. There was a significantly higher nonhospitalization period, a proxy for quality of life, for patients in the carboplatin-paclitaxel arm. Based on these results, and on the feasibility of administration, carboplatin-paclitaxel is recommended as a treatment option for recurrent, metastatic, or persistent cervical cancer.

RECOMMENDATION 3

Bevacizumab in combination with cisplatin-paclitaxel is recommended for a specific subset of the target population, which includes only patients that match the characteristics of the GOG-0240 study population [4]. Carboplatin may be substituted for cisplatin in this patient population, based on the justification given under Key Evidence and Justification below.

The subset includes patients with primary stage IVB (has spread to parts of the body away from the cervix, such as the liver, intestines, lungs, or bones) [5], recurrent, or persistent disease not amenable to curative treatment with surgery and/or radiotherapy, who have performance status scores of ≤ 1 , adequate renal, hepatic, and bone marrow function, and not including those patients previously treated with chemotherapy for recurrence or those with nonhealing wounds, active bleeding conditions or inadequately anticoagulated thromboembolism. In addition, GOG-0240 did not include patients with stage IIIB cancer (local extension to pelvic sidewall) or IVA cancer (invasion into bladder or rectum). For more details on the GOG-0240 patient population, see the study details provided at clinicaltrials.gov [6].

Contraindications to bevacizumab include:

- Uncontrolled hypertension
- Arterial thromboembolic events within last 6 months (includes cerebrovascular accident [CVA], transient ischemic attack [TIA], or myocardial infarction [MI])
- Surgical procedure within 28 days
- Full dose anticoagulation

Summary of Key Evidence and Justification for Recommendation 3

Results detected a significant overall survival rate advantage of chemotherapy with cisplatin (50 mg/m^2) and paclitaxel (135 or $175 \text{ mg/m}^2 \text{ d1}$) or topotecan ($0.75 \text{ mg/m}^2 \text{ d1}$ to d3) and paclitaxel ($175 \text{ mg/m}^2 \text{ d1}$) with bevacizumab (15 mg/kg of body weight d1) (HR), 0.71 ; $98\% \text{ CI}$, $0.54\text{-}0.95$; $p=0.004$, one-sided) versus these chemotherapy options without bevacizumab. Cycles were repeated at 21-day intervals. There was also a significant difference in OS for cisplatin-paclitaxel with bevacizumab compared with cisplatin-paclitaxel without bevacizumab (median OS: 17.5 versus 14.3 months, HR, 0.68 ; $95\% \text{ CI}$, $0.48\text{-}0.97$; $p=0.04$, one-sided). Patients in the bevacizumab arm experienced more hypertension of grade 2 or higher, thromboembolic events of grade 3 or higher, and gastrointestinal fistula of grade 3 or higher; however, no significant differences in quality of life were detected. As in GOG-0204, patients in this trial had a performance status of ≤ 1 . The discontinuation rate was 25% with patients in the bevacizumab group versus 16% of patients in the group that did not receive bevacizumab.

Although GOG-0240 tested bevacizumab with cisplatin and paclitaxel, the noninferiority of carboplatin-paclitaxel demonstrated in JCOG-0505, its more favourable toxicity profile and ease of administration, as well as its demonstrated efficacy in other disease sites [7] provide support for the recommendation for carboplatin.

Qualifying Statement for Recommendation 3

There may be a risk of thrombocytopenia with the combination of carboplatin and bevacizumab. However, estimates of the level of risk for this adverse event are not available, as the combination was not tested in the patient population for this guideline.

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Updating

All PEBC documents are maintained and updated through an annual assessment and subsequent review process. This is described in the PEBC Document Assessment and Review Protocol, available on the CCO website at: <https://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=122178>

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