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Evidence-Based Series 4-8 Version 4 REQUIRES UPDATING

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

Systemic Therapy for Advanced or Recurrent Endometrial Cancer, and Advanced or Recurrent Uterine Papillary Serous Carcinoma

Members of the Expert Panel on Endometrial Cancer or Uterine Papillary Serous Carcinoma

An assessment conducted in November 2020 indicated that Guideline 4-8 Version 4 REQUIRES UPDATING. 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 4-8 Version 4 is comprised of 2 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/501

Section 1: Clinical Practice Guideline (ENDORSED)
Section 2: Document Assessment and Review

July 23, 2019

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please visit the CCO website at http://www.cancercare.on.ca/
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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original version 2004	1966-2004	Full Report	Web publication	NA
Reviewed Version 2 March 2014	2004 to December 2013	New data found in Appendix A	Updated web publication	2004 recommendations are **ENDORSED**
Reviewed Version 3 June 6 2017	December 2013 to March 2017	New data found in Appendix B	Updated web publication	2004 recommendations are **ENDORSED**
Current Version 4 July 2019	March 2017 to March 2019	New data found in Section 2: Document Assessment and Review	Updated web publication	2004 recommendations are **ENDORSED**

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Evidence-based Series 4-8 Version 4: Section 1

Systemic Therapy for Advanced or Recurrent Endometrial Cancer, and Advanced or Recurrent Uterine Papillary Serous Carcinoma

Practice Guideline Report #4-8

C. Gawlik, M. Carey, W. Faught, M. Fung Kee Fung, A. Chambers, and members of the Gynecology Cancer Disease Site Group

Report Date: August 17, 2004

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 2: Document Assessment and Review for a summary of updated evidence published between 2017 and 2019, and for details on how this Clinical Practice Guideline was ENDORSED.

SUMMARY

Guideline Questions

1. What are the chemotherapeutic and hormonal therapy options for women with advanced or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas)?
2. What are the chemotherapeutic options for women with advanced or recurrent uterine papillary serous carcinoma?

Target Population

This practice guideline applies to adult patients diagnosed with advanced stage or recurrent endometrial cancer (excluding sarcomas and squamous cell carcinomas) or uterine papillary serous carcinoma.

Recommendations

For women with advanced or recurrent endometrial cancer:

- Combination chemotherapy is favoured over single agent chemotherapy because of higher response rates.
- Paclitaxel in combination with cisplatin/doxorubicin chemotherapy improves both response rate and median survival; however, the use of this three-drug combination is associated with increased toxicity.
- Hormonal therapy may be a therapeutic option for those patients with minimal symptoms or non-life threatening advanced or recurrent endometrial cancer.

For women with uterine papillary serous carcinoma:

- Evidence supporting or refuting various chemotherapy regimens for uterine papillary serous carcinoma is limited.
- Patients should be encouraged to participate in randomized trials.

Qualifying Statements:

- The decision to use the three-drug combination, consisting of cisplatin/doxorubicin/paclitaxel, should be made with consideration of both the greater toxicity and the three-month increase in median survival time in comparison with the two-drug doxorubicin/cisplatin regimen. However, recent data suggest no benefit to the three-drug combination in terms of recurrence-free survival and was associated with increased toxicity.
- For uterine papillary serous carcinoma treatment, the most studied regimen is a paclitaxel/platinum combination. The addition of paclitaxel in small, non-comparative studies is associated with improved response rates and survival compared to non-platinum containing regimens.

Added to Endorsement in June 2017:

- As mentioned in the Qualifying Statements above, there are data suggesting that a taxane-platinum drug combination has similar efficacy with better toxicity when compared with the three-drug paclitaxel/cisplatin/doxorubicin combination. The Expert Panel recognizes that this evidence comes from an abstract of an interim analysis of a phase III RCT with no full publication and does not meet the criteria for inclusion in this review. However, practice has changed in light of this evidence with preference for a taxane-platinum drug combination although the three-drug combination is still an option.

Added to Endorsement in July 2019:

- There has been one small randomized phase II study showing a benefit of adding trastuzumab to carboplatin/paclitaxel in patients with overexpression of Her2/Neu in advanced (stage III or IV) or recurrent uterine serous carcinoma. Please see Section 2 for further details.

Methods

Entries to MEDLINE (1966 to April 2004), CANCERLIT (1975 to October 2002), and Cochrane Library (2004, Issue 1) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1997 to 2003) were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by four members of the Practice Guidelines Initiative's Gynecology Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Gynecology Cancer Disease Site Group, which comprises gynecologic oncologists, medical oncologists, radiation oncologists, an oncology nurse, a pathologist, and patient representatives.

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, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Seventeen randomized trials (including six abstracts and four phase II randomized trials) provided the evidence for systemic therapy of advanced or recurrent endometrial cancer. There were no randomized trials identified that compared systemic therapy to a control group of patients who received no treatment.
- Limitations of the evidence include: heterogeneous patient populations with respect to histology; type of previous treatment (surgery, radiation, chemotherapy, or hormonal therapy); results that are still maturing; and non-comparable outcome measurements.
- Chemotherapeutic options studied for the treatment of advanced or recurrent carcinoma of the endometrium have included single-, double-, and triple-agent therapies. There is limited information available on quality of life and meaningful survival data.
- Single-agent chemotherapy has reported response rates as follows: doxorubicin 17-27% and platinum agents 21%.
- For double-agent chemotherapy, randomized trials of doxorubicin/cisplatin reported response rates ranging from 28-45%, other agents in combination with doxorubicin reported response rates of 30% (cyclophosphamide) and 43% (paclitaxel).
- A randomized trial reported a 57% response rate in the doxorubicin/paclitaxel/cisplatin arm compared to 34% in the doxorubicin/cisplatin arm ($p < 0.01$).
- One randomized trial has compared doxorubicin/cisplatin to whole abdominal radiotherapy and preliminary reports indicate that doxorubicin/cisplatin is more beneficial than radiotherapy in patients with advanced endometrial cancer in terms of overall survival and progression-free survival ($p<0.01$). However, recurrence rates are still high (55%) in both treatment arms.
- Neuropathy, hematological, and gastrointestinal toxicities were the most common adverse effects reported; toxicity increased in incidence with the increase in the number of agents used.
- One randomized trial comparing two dosages of medroxyprogesterone acetate (hormonal therapy) for advanced or recurrent endometrial cancer detected that patients receiving a lower dosage of medroxyprogesterone acetate had significantly increased overall survival ($p=0.026$) and response rate ($p<0.05$) than patients receiving a higher dosage. Hormonal agents were well tolerated: adverse effects were reported at less than 5%.
- Four non-comparative trials (two retrospective and one abstract) provided the evidence for systemic therapy of advanced or recurrent uterine papillary serous carcinoma. Response rates in the four small non-comparative studies ranged from 50-89%

Future Research

In terms of future studies, it is important to be able to control for prognostic factors that affect outcome in these patient populations. Patients should be properly stratified with respect to their disease status (advanced versus recurrent), the amount of previous treatment, type of previous treatment (radiation or chemotherapy), and disease recurrence either in or out of the radiated field. Patients with uterine papillary serous carcinoma should be analyzed separately. Results relating to systemic therapy should be first assessed and proven in those patients with measurable disease so that an accurate assessment of any prolongation in disease-free survival can be made with reasonable assurance that these improvements are due to treatment. Treatment-related toxicity must be studied very carefully in the future in this patient population in order to ensure that the treatment itself has acceptable morbidity in relation to the patient's quality of life, as median survival is generally limited and rarely more than a year in this patient population. Survival, response and toxicity should be studied with regard to impact on quality of life. Comparing tumour responses for both chemotherapy and hormonal agents, stratified by grade, would provide valuable data for making treatment decisions.

Added to Endorsement in July 2019:

Immunotherapy is an emerging treatment, particularly in patients with tumours with high microsatellite instability, and should be addressed in future guidelines as studies become available.

For further information about this practice guideline report, please contact Dr. Michael Fung Kee Fung, the lead author, through the PEBC at:
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The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

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