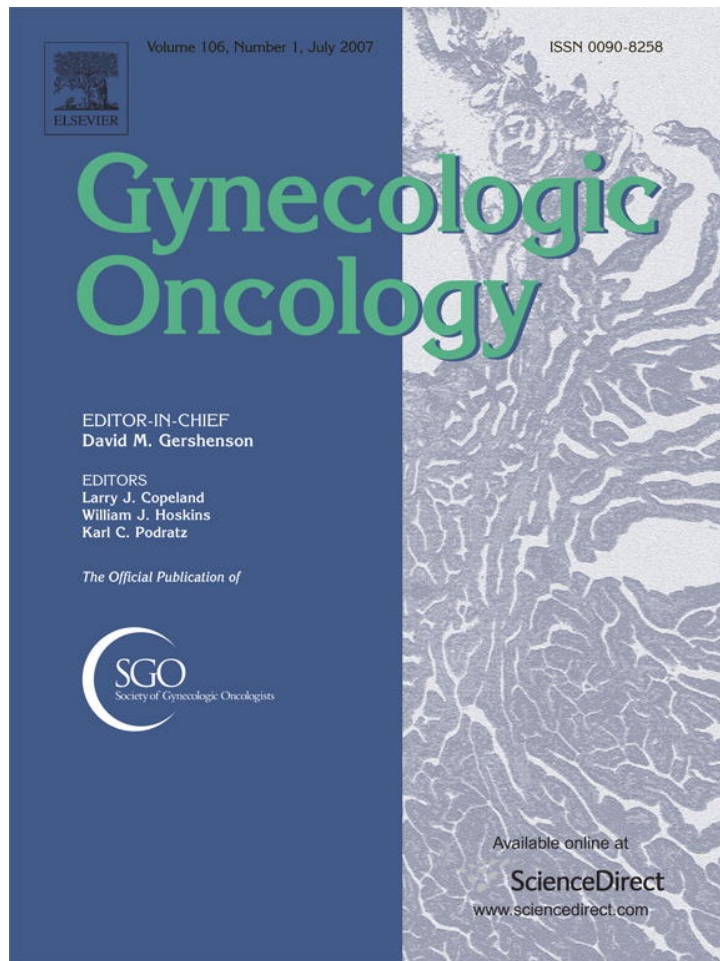


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Gynecologic Oncology 106 (2007) 181–192

Gynecologic
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Use of systemic therapy in women with recurrent ovarian cancer—Development of a national clinical practice guideline

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Received 20 December 2006

Available online 11 May 2007

Abstract

Objective. To develop a guidance document concerning the use of systemic therapy for women with recurrent ovarian cancer that would be applicable for the Canadian health care system. This will be done using a standardized systematic review process, guideline evaluation instruments, multi-disciplinary expert consensus opinion and evidence-rating systems.

Data selection. The primary data sources were MEDLINE, National Guideline Clearinghouse and Cochrane Library.

Methods. Clinical practice guidelines, technology assessments, systematic reviews and randomized controlled trials addressing systemic therapy for women with recurrent ovarian cancer were eligible.

Data extraction. Data was identified and extracted by the methodology team and reviewed by the authors. Results were reviewed and discussed by members of an expert working group comprised of a multidisciplinary and geographic divergent group of practitioners.

Data synthesis. The existing 7 practice guidelines underwent formal evaluation for quality, currency and content using the AGREE tool. Recommendations with evidence-ratings were developed. This data was used by a pan-Canadian panel in an informal consensus process, which resulted in the initial draft of a guideline. The guideline team reviewed the draft and made further edits to ensure the guideline's appropriateness for a national context. Practitioner feedback was requested from 165 health care providers who treat ovarian cancer from across Canada. Overall response rate was 37% and was very positive. Comments were reviewed and the guideline was edited appropriately.

Conclusion. The development of a national practice guideline on the use of systemic therapy for recurrent ovarian cancer was feasible using systematic literature review, expert consensus, guideline evaluation instruments, evidence-rating systems, independent internal and external review measures and final approval by a national discipline specific society (GOC). Recommendations for practice are offered.

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Keywords: Recurrent ovarian cancer; Systemic therapy; Guidelines

Introduction

Research dollars are typically allocated to basic and clinical research of gynecological cancer and translational research between these fields. Although appropriate, the expansion of a research trajectory to include studies that translate knowledge

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gained into strategies that facilitate decision-making is also important. Treatment decisions made by clinicians and patients are not always in keeping with the most current and compelling evidence [1,2]. Further practice of gynecologic care varies across Canada with respect to the extent of surgery, chemotherapy offered and radiation prescribed. In part, this is based on training, continuing medical education and provincial policies toward drug reimbursement and access. However, differences can also be attributed to the increasingly willingness of women to seek treatment for modest gains. For example, while there are emergent drug therapies to address recurrent ovarian cancer, at this point, the main focus in treating the disease is directed toward improved quality of life, an perhaps, duration of survival.

Clinical practice guidelines are one example of a recognized knowledge transfer tool to help eliminate undesired variations in care. Developing high quality evidence-based guidelines, however, is resource intensive. An important component of a national guideline is to ensure that the document is comprehensive enough to apply to differing provincial contexts and to assess its applicability in the clinical world. Thus, a fine balance must be reached between providing national direction while allowing for provincial flexibility.

To address these challenges and to move forward on a quality improvement agenda of gynecologic oncology care, a collaboration between the Society of Gynecologic Oncologists of Canada (GOC) [3] in the Canadian Strategy for Cancer Control (CSCC) was established to capitalize on guideline adaptation processes [4–6] to create a guidance document regarding management of recurrent ovarian cancer.

The GOC is a national group looked to by practitioners from across the country for guidance [3]. The CSCC clinical practice guidelines action group, has developed an adaptation methodology which takes advantage of existing guidelines and assists expert panels in customizing a guideline appropriate for the context of use. Thus, this guideline will create and apply best evidence knowledge to help inform clinical decisions. This paper focuses on the development of the guideline using an adaptation process, and how the guideline will be used to potentially address variations in care and need for guidance by policy makers in an era of cost constraint.

Methods

Process of guideline adaptation

In order to facilitate the process of guideline adaptation, the GOC chose to use a guideline adaptation process developed by the CSCC Clinical Practice Guidelines Action Group (CPG-AG) in conjunction with leading researchers in the field of guideline adaptation [3,4]. The following describes the process followed by the panel in deriving guidance on systemic therapy for women with recurrent ovarian cancer.

Expert reviewer panel deliberations

The expert reviewer panel was populated with representation from and partnership with the CPG-AG; Gynecology Oncology Guideline Panels from provincial cancer agencies, and clinicians including gynecologic, medical and radiation oncologists from across Canada. Present were experts in the clinical, research, methodological, and knowledge translation arenas (14 clinical

specialists, 4 methodological specialists). This representation would minimize bias and ensure that the panel was diverse enough to capture all the important perspectives [4,5]. Panel members met to deliberate. All completed a signed conflict of interest declaration.

Guideline team

A small writing group (comprised of one methodological and five clinical experts) and an expert reviewer worked collaboratively to create the guideline. The writing group oversaw the day-to-day guideline adaptation process and writing of the drafts with the larger expert reviewer group providing feedback regarding topic selection and recommendation development.

Choice of topic

Recurrent ovarian cancer was identified as the quality care issue of choice because it has been identified as a priority topic by the GOC membership. Further, it was recognized that large variations across Canada exist in delivery of systemic therapy even where well-conducted trials define optimal care. Finally, there are different gynecologic oncology clinical practice guidelines that address this topic, however, in some cases the advice runs contrary across reports.

Search for evidence

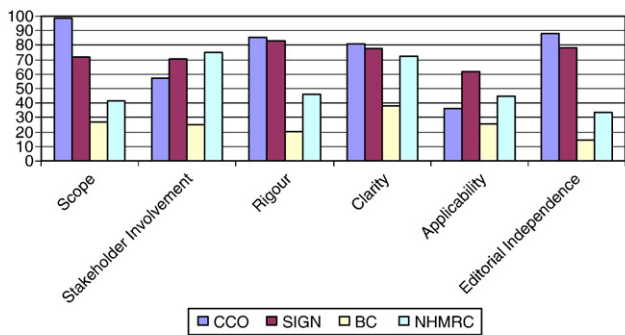
A systematic search of existing practice guidelines, systematic reviews and randomized controlled trials was undertaken. The team searched MEDLINE, the World Wide Web (using Google), the Canadian Coordinating Office on Health Technological Assessment website, the Cochrane Collaboration website, guideline clearinghouses (National Guideline Clearinghouse, Canadian medical Association, Guidelines International Network), known guideline developer's websites (e.g. National Institute of Clinical Excellence UK; Centre for Reviews and Dissemination UK; Ministry of Health Singapore; World Health Organization; Standards, Options and Recommendations France; New Zealand Guidelines Group, National Health and Medical Research Council Australia; Society of Gynecologic Oncologists USA, Agency for Health Research and Quality USA; Department of Defense USA) as well as references of published guidelines for guidelines on recurrent ovarian cancer. The terms used for MEDLINE searches were purposefully broad; practice guidelines, reviews, standards, consensus and ovarian neoplasms. Those used for the WWW search included ovarian cancer, recurrent ovarian cancer, practice guidelines and clinical practice guidelines. The following inclusion and exclusion criteria were used: only guidelines that were dated from 1995 to 2005 and published in English or French were considered. Guidelines without references and those authored by a single individual (not on behalf of a group) were not considered. Two guidelines, one from Cancer Care Ontario (CCO) [7] and one from the Scottish International Guidelines Network (SIGN) [8] were chosen a priori for inclusion. They also emerged from the systematic review.

Guideline assessment

The practice guidelines were assessed for quality using the "Appraisal of Guidelines Research and Evaluation" (AGREE) tool [9] (www.agreetrust.org). The tool assesses six quality domains including scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability and editorial independence. At least 2 individuals should score each guideline on a 4-point scale. A summary question addresses whether the guideline should be strongly recommended, recommended, would not recommend or unsure. An assessment of currency of retrieved guidelines [10] was undertaken by the methodologists on the team.

Preparation of the recommendations matrix

In order to easily identify similarities and differences in the recommendations of each guideline, the methods team compiled the recommendations from each of the guidelines into a Recommendations Matrix — a table of recommendations grouped together by topic. Where possible, the level of evidence associated with a particular recommendation was provided (Appendix A); otherwise this information was left blank.



	Scope	Stakeholder Involvement	Rigour	Clarity	Applicability	Editorial Independence
CCO [7]	98.41	57.14	85.71	80.95	36.51	88.1
SIGN [8]	71.43	70.24	82.99	77.38	61.9	78.57
BC [11]	26.98	25	20.41	38.1	25.4	14.29
NHMRC [12]	41.67	75	46.03	72.22	44.44	33.33

CCO - Cancer Care Ontario guideline

SIGN - Scottish International Guidelines Network guideline

BC - BC Cancer Agency Management Protocol

NHMRC - National Health and Medical Research Council (Australia) guideline

Fig. 1. AGREE scores (6 raters for the CCO, SIGN, BC guidelines, 3 raters for the NHMRC guideline).

External review

The draft guideline, a cover letter from the president of the GOC and a survey were mailed to all Canadian practitioners involved in the care of women with ovarian cancer. A reminder was sent approximately 1 month after the mailing of the initial package. The survey asked for comments on the guideline and also contained items evaluating the methods used in the drafting of the guideline, whether the recommendations are applicable in the practitioner's context, whether the recommendations should be approved as a guideline, and whether the practitioner would use the guideline in his or her practice.

The document including results from the external review was then vetted through the executive of the GOC for final approval.

Results

Retrieval of guidelines

Four guidelines were retrieved. The CCO draft guideline [7] was the only guideline that focused on recurrent ovarian cancer. The SIGN guideline [8] included a section on recurrent ovarian cancer within a larger guideline on ovarian cancer management. The BC Cancer Agency management protocol for ovarian cancer [11] was included as it is a widely used protocol. The National Health and Medical Research Council (Australia) guideline [12] included a small section on recurrence. Panel members were also provided with the following supporting documents: an National Cancer Institute Physician Data Query (USA) with a section on recurrence [13], a National Institute on Clinical Excellence (UK) document on Paclitaxel, Pegylated Liposomal Doxorubicin Hydrochloride and Topotecan for second-line or subsequent treatment [14], and two care paths (National Comprehensive Cancer Network, U.S.A. [15] and MD Anderson Cancer Center, U.S.A. [16]).

Guidelines assessment — quality and content

Six panel members returned scores on two or more of the documents. Scores for the dimensions of the AGREE instrument ranged from 41% to 98% for the CCO guideline, from 57% to 81% for the SIGN guideline, from 17% to 36% for BC Cancer Agency management protocol, and from 33% to 75% for the NHMRC guideline (Fig. 1). With respect to overall assessment, the CCO guideline was most strongly recommended, followed by the SIGN guideline (Table 1).

Guideline currency was not an issue with respect to the CPGs reviewed by panel members. The CCO guideline is still in draft format, and the BC Cancer Agency management protocol is a living document. The status of both the SIGN and NHMRC guidelines is listed as 'current' on their respective websites. The SIGN guideline was published in October 2003, and the NHMRC guideline was published in 2004. The recommendations published in these guidelines were all considered up-to-date and valid by panel members.

Synthesis of the evidence and the development of recommendations

The AGREE scores provided panel members with a sense of the quality of development as reported in the guidelines. However, the panel discussion focused mainly on the individual recommendations from each guideline. On the basis of the systematic review of the evidence, a quality assessment of identified guidelines (Fig. 1, Table 1), and expert evidence interpretation, the panel felt they could not adopt any one guideline in its entirety. The panel decided to synthesize the evidence, which evolved from the recommendation matrix (Table 2) in terms of the general principals, platinum sensitive disease, platinum resistant disease, platinum refractory disease and principals for stopping chemotherapy. At the end of this meeting, a list of tentative recommendations was drafted. The guideline team would meet to refine the recommendations and content of the final document.

During the months that followed, there were opportunities for feedback on the draft guidelines by virtue of electronic correspondence and telephone conferences. In those areas where there was insufficient or conflicting evidence on which

Table 1
Overall assessment ratings by reviewers using the AGREE tool

	Strongly recommend (%)	Recommend with alterations (%)	Would not recommend (%)	Unsure (%)	Total number of reviewers
CCO [7]	60	40			5
SIGN [8]	33	33	33		6
BC [11]			60	40	5
NHMRC [12]	50		50		2

CCO — Cancer Care Ontario guideline.

SIGN — Scottish International Guidelines Network guideline.

BC — BC Cancer Agency Management Protocol.

NHMRC — National Health and Medical Research Council (Australia) guideline.

Table 2
Recommendations matrix — recurrent ovarian cancer

	CCO recurrent ovarian [7] ^a (draft guideline)	SIGN epithelial ovarian [8] (guideline)	BC cancer [9] (management guidelines)	NHMRC [10] (guideline)	NICE [12] (technology appraisal)	NCCN [15]	NCI PDQ [13]
Context:							
Clinical trials	<i>The body of evidence which informs clinical recommendations is sparse and incomplete, thus, all pts with recurrences are encouraged to participate in clinical trials. (Level 3, Recommendation C)</i>	<i>Pt care should be discussed within the multidisciplinary team and where possible pts should be entered into appropriate clinical trials. (Good practice point)</i>			<i>*note: the tech appraisal only reviewed paclitaxel, PLDH and topotecan</i>		
Individual assessment	<i>Each pt needs to be assessed individually to determine optimal therapy for her in terms of recurrence, sensitivity to platinum and toxicity. (Level 3, Recommendation C)</i> <i>Women may repeatedly be considered platinum-sensitive and may benefit from more than one line of therapy. (Level 2, Recommendation B)</i>				<i>Within the recommendations, the choice of trt for second line or subsequent chemotherapy should be made after discussion between the responsible clinician and the pt about the risks and benefits of the options available</i>		
Role of chemotherapy		Chemotherapy for recurrent ovarian cancer should be regarded as palliative in intent and should be reserved for symptomatic recurrence of disease. (B)					
Quality of life		Women should be given accurate information on their likely response to chemotherapy, including adverse effects, so they can make a decision about whether or not to proceed with trt. (D) The impact of chemo toxicities on patients' QOL must be balanced against their anticipated response to trt. (D)					

Patients with platinum-sensitive recurrences

Combination therapy	Combination chemotherapy is preferred over single agent chemo. Either paclitaxel/carboplatin or gemcitabine/carboplatin is favored over carboplatin alone in terms of overall survival and response rate. (Level 1, Recommendation A)	Symptomatic platinum-sensitive cancer recurrence can be treated with further platinum and paclitaxel. (B) <i>Cautious clinical judgement should be used when considering the use of platinum and paclitaxel in pts with symptomatic platinum-sensitive cancer recurrence after a trt-free interval of 6–12 mths. (gd practice pt)</i>	If pts have shown a high-quality and long-lasting response to initial platinum-based trt, then carboplatin can be used with a good chance of secondary response.	Retreat with carboplatin (lvl of evidence IV). <i>Principle of therapy for relapsed disease should be that the potential utility of single agent carboplatin should be exhausted before moving on to other agents.</i>	<i>Paclitaxel in combination with a platinum-based compound (carboplatin or cisplatin) is recommended as an option for second line (or subsequent) trt of women with platinum sensitive or partially platinum sensitive advanced cancer except in women allergic to platinum based compounds.</i>	<i>Recent evidence suggests that combination chemo may be superior to single agent therapy in this situation although sequential therapy may provide the same results. Alternatively pts can be treated with single agent taxane or platinum and then crossed over to the other agent as dictated by clinical response. For stage III and IV patients with partial responses, recurrence regimens include single agent therapy or a combo of a taxane and a platinum, recurrence chemo or IP therapy.</i>	<i>Carboplatin+paclitaxel resulted in progression free survival (Level of evidence IiiA)</i>
Single agent recommendations (platinum compound)	If combination therapy is not indicated, it is the opinion of the Gynecology Cancer DSG that a single platinum compound (ie., carboplatin) is preferred over a non-platinum compound. (Level 3, Recommendation B)				<i>PLDH is recommended as an option for the second line (or subsequent) trt of women with partially platinum sensitive, platinum resistant or platinum refractory advanced cancer and for women who are allergic to platinum based compounds.</i>		Re-treatment with cisplatin or carboplatin should be considered.

(continued on next page)

Table 2 (continued)

	CCO recurrent ovarian [7] ^a (draft guideline)	SIGN epithelial ovarian [8] (guideline)	BC cancer [9] (management guidelines)	NHMRC [10] (guideline)	NICE [12] (technology appraisal)	NCCN [15]	NCI PDQ [13]
Patients with platinum-sensitive recurrences							
Other agent recommendations	If a platinum compound is not indicated, then it is the opinion of the Gynecology Cancer DSG that trt decisions should be based on toxicity and ease of administration information. (Level 3, Recommendation C) <i>Only one comparative randomized trial in the sensitive group has compared two non-platinum compounds (PLD vrs topotecan). Neither compound has been compared to carboplatin. (Level 1, Recommendation B)</i>						
Patients with platinum-resistant recurrences							
Paclitaxel	There is no evidence to support or refute the use of more than one line of chemotherapy in patients with platinum-resistant recurrences. (Level 3, Recommendation C)	<i>The optimal agents in platinum-resistant disease have yet to be defined and trt should be based on specialist judgement. (gd practice pt)</i>	Pts with progressive platinum-refractory ovarian cancer may benefit from taxol if this agent was not a component of primary trt.	<i>An argument can be made for not considering further treatment. In patients with relapsed ovarian cancer, quality of life must be a major component of assessment.</i>	<i>Single agent paclitaxel is recommended as an option for the second line (or subsequent) trt of women with platinum refractory or platinum resistant advanced cancer or for women who are allergic to platinum based compounds.</i>	<i>Supportive care OR recurrence regimen (see next page)</i>	<i>Trt with paclitaxel should be considered</i>

Topotecan
Options include non-platinum drugs such as topotecan and doxorubin. (Level 3, Recommendation B)

PLDH(see above)
Topotecan is recommended as an option for second line (or subsequent) trt only for those women with platinum refractory or platinum resistant advanced cancer or those who are allergic to platinum based compounds for whom PLDH and single agent paclitaxel are considered inappropriate.

Salvage chemotherapy and other options

Tamoxifen should be considered in pts for whom chemotherapy is not appropriate. (C)

Taxol is not indicated for those with asymptomatic and/or non-progressive disease following conventional therapy or those with bowel obstructions or a marked impairment of performance status. Other drugs potentially effective in this situation are oral etoposide, gemcitabine, topotecan and vinorelbine.

In trt of ovarian cancer no longer sensitive to platinum, topotecan and PLDH have some efficacy in terms of response rate and survival times. Tamoxifen can be considered where chemo is inappropriate

Acceptable recurrence modalities: tamoxifen oral etoposide vinorelbine paclitaxel docetaxel topotecan altretamine PLDH carboplatin cisplatin oxaliplatin gemcitabine cyclophosphamide melphalan radiation therapy

PLD, topotecan, PLD and topotecan, gemcitabine, fluorouracil and leucovorin, tamoxifen, etoposide, ifosfamide, HMM, capecitabine — have all shown to have activity in refractory ovarian cancer
Secondary cytoreduction — no studies to show survival advantage.
Surgical intervention may improve QOL when disease-related symptoms can be abrogated.

Pts who progress on 2 consecutive single agent regimens without evidence of clinical benefit are unlikely to benefit from additional chemo and may be offered best supportive care or clinical trial.

to base the recommendations, expert consensus opinion was used to guide the decision making process. The guideline team decided that for both platinum sensitive and platinum resistant disease explanatory paragraphs needed to be attached to the recommendations. These explanations represent the result of discussions by the panel on various associated issues. A draft guideline was produced, edited and then circulated to all members of the review panel for feedback and approval prior to gathering feedback from an external review.

Review process

External review

Feedback on the draft recommendations was sought from 165 practitioners who treat ovarian cancer from across Canada. The overall response rate was 37% (Table 3). Responses were received from each province in Canada at a rate of 20–100% by province. The main respondent group was gynecologic oncologists (62.5%), followed by medical oncologists (25%), radiation oncologists and internal medicine practitioners (3% each) and finally obstetricians/gynecologists and psychosocial oncology (1% each).

Comments on the draft guideline were received from 29 of the respondents. Half of these represented general comments, the other half were suggestions for changes to the document. Of the suggestions, eight were addressed in the addition of a section entitled “Scope of the guideline” clarifying the purview of the guideline. Three reviewers brought to the attention of the panel the recent publication of an article where previously only the abstract was available. Other suggestions resulted in the addition of supporting evidence to the document, most references for Phase II trial of gemcitabine, etoposide and vinorelbine and a listing of currently active Phase 3 trials. An addition was made to only one recommendation, with clarification of treatment interval.

National practice guideline approval process

As a final quality control measure prior to publication, the guideline was circulated to the members of the GOC executive. This is a multidisciplinary group with expertise in clinical cancer care, basic science research and health methodology. The practice guideline report was circulated to 12 members for review and approval. The document was unanimously approved with no modifications needed. The final guideline can be viewed on www.g-o-c.org.

The final guideline

Question:

What are the clinical treatment principles of managing women with recurrent ovarian cancer using systemic therapy?

Patient population:

These recommendations apply to women with recurrent epithelial ovarian cancer including women with platinum sensitive, platinum resistant and platinum refractory disease.

Guideline target population:

The guideline is to be relevant to physicians who provide systemic therapy to women with ovarian cancer (ie., gynecologic and medical oncologists or their delegates), provincial cancer agencies, pharmaceutical industry and Provincial Drug Agencies.

Recommendation statements:

1. Each patient is unique in her disease. Patients must be considered as a whole when making treatment recommendations. The basic principle is to use the most effective regimen or single agent. If the alternatives are equally effective, then choose treatment based upon toxicity, convenience and availability.
2. Whenever clinical trials are available, all patients should be offered participation in these trials. The outcome of systemic therapy for recurrent ovarian cancer is not cure. The goals of

Notes to Table 2:

Regular text=Recommendation in guideline *Italicized text=qualifying statement or trt option in a document other than a CPG.*

Pt=patient Trt=treatment PLDH=pegylated liposomal doxorubicin hydrochloride DSG=disease site group QOL=quality of life.

Definitions of platinum sensitive and platinum resistant as used in the resources.

Platinum sensitive

CCO — relapse after 6 months

SIGN — relapse after 6 months

BC Cancer Agency — relapse after 12 months

NHMRC — relapse after 6 months

NICE — relapse after 6+ months

NCI — relapse after 5–12 months minimum

NCCN — complete remission and relapse 6+ months after starting chemo

Platinum resistant

CCO — no response to initial platinum based chemo, complete or partial response followed by progression while still on chemo, response then relapse 6 months after stop of chemo

SIGN — treatment free interval less than 6 months

BC Cancer — less than complete clinical response, 6 months or less interval between treatment and relapse

NHMRC — patients who do not respond to initial therapy or who progress during initial chemo

NICE — Resistant=relapse within 6 months of completion of initial platinum based chemo/Refractory=no response to initial platinum based chemo

NCI — progression of disease while on platinum-based regimen or has recurred shortly after completion of regimen

NCCN — progression or stable disease on primary chemo or complete remission and relapse less than 6 months after stopping chemo

^a Levels of Evidence and Recommendation from Appendix A.

Table 3
Practitioner feedback — recurrent ovarian cancer (*n*=60 usable out of 165 surveyed)

Question	Responses				
	Yes	No	Unsure		
1. Are you responsible for the care of patients for whom this draft guideline report is relevant?	60	4			
	Strongly agree		Neither agree or disagree	Strongly disagree	Blank/other
2. The rationale for developing a guideline, as stated in the "Choice of Topic" section of this draft report is clear.	29	22	3	1	5
3. There is a need for a national guideline on this topic.	31	20	6	3	
4. The lit search is relevant and complete.	23	30	7		
5. I agree with the methodology used to summarize the evidence in this draft guideline.	17	31	8	4	
6. The results are interpreted according to my understanding of the data.	23	34	1	2	
7. The draft recommendations are clear.	21	31	6	1	1
8. I agree with the draft recommendations as stated.	19	35	3	3	
9. The draft recommendations are suitable for the patients for whom they are intended.	21	35	3	1	
10. The draft recommendations are too rigid to apply to individual patients.		1	10	31	10
11. When applied, the draft recommendations will produce more benefits than harms for patients.	14	27	17	1	1
12. The draft guideline report presents options that will be acceptable to patients.	12	36	10	1	1
13. To apply the draft recommendations will require reorganization of services/care in my practice setting.	1	2	7	25	25
14. To apply the draft recommendations will be technically challenging.	1	1	7	24	27
15. The draft recommendations are too expensive to apply.		1	8	29	21
16. The draft recommendations are likely to be supported by a majority of my colleagues.	13	38	6	2	
17. If I follow the draft recommendations, the expected effects on patient outcomes will be obvious.	4	20	27	8	1
18. The draft recommendations reflect a more effective approach for improving patient outcomes than is current usual practice.	2	7	12	5	If same as current practice, tick NA. 34
19. When applied, the draft recommendations would result in better use of resources than current usual practice.	2	10	11	5	If same as current practice, tick NA. 31
20. I would feel comfortable if my patients received the care recommended in the draft guideline.	21	34	4	1	
21. This draft report should be approved as a practice guideline.	20	27	9	3	1

treatment should be to improve quality of life (or symptom free interval or symptom intensity), or increase the progression free interval.

- Women can be subdivided into three groups predictive of response to further platinum analogues: platinum-refractory (their cancer progresses upon treatment) who will not respond to platins; platinum-resistant (cancer recur objectively within 6 months of completing treatment) — they have a 10% response rate to further platins; and platinum-sensitive (recur more than 6 months after completing treatment) — they have a 30% predicted response rates with platinum retreatment. These latter two definitions are arbitrary and merely reflect an artificial cut point chosen to best delineate higher and lower response rates to subsequent treatment.
- Repeated courses of chemotherapy can be effective in selected patients. As a principle, re-utilize the previous effective drug(s) until progression, or undue toxicity

adversely impacting quality of life or treat for a defined number of cycles.

The principles specific to platinum sensitive disease are that whenever clinical trials are available, all patients should be offered participation in these trials. Patients who experience a long treatment free interval of at least 1 year after exposure to platinum based chemotherapy should have the opportunity for retreatment with either platinum based combination or monotherapy. Platinum based combination therapy should be considered in these patients. Single agent platinum therapy is preferable for those patients who have experienced significant toxicities (unless the platin was the responsible agent). If a platinum compound is not warranted due to toxicity, then choice of systemic agent should be based on their toxicity profile, ease of administration, and availability.

There are currently two randomized trials which have shown an advantage of re-treatment with combination

platinum based chemotherapy versus monotherapy. In ICON 4, 802 patients relapsing after more than 6 months of treatment free disease were randomized to paclitaxel/platinum or platinum alone chemotherapy [17]. The majority of participants had more than 12 month platinum free interval (75%), with 25% relapsing from 6–12 months after adjuvant platinum based therapy. Only 42% of the patients in this trial had been exposed to first line taxane therapy. After 42 months of follow-up, there was a survival difference in favor of platinum taxane (HR 0.82 95%CI 0.69–0.97 and median survival increase of 5 months, 29 vs 24 months). Median progression free survival was 13 and 10 months.

In the AGO trial, 356 women relapsing at least 6 months after adjuvant chemotherapy were randomized to gemcitabine–carboplatin or carboplatin alone [18]. Approximately 40% of women had recurred within 6–12 months and 60% after 12 months. With median follow-up of 17 months, the progression free survival was 8.6 months (95%CI 7.9–9.7 months) vs 5.6 months (95% 5.2–7.1 months) in favor of the combination arm. Median survival was 18 months (95% CI 16.2–20.2 months) versus 17.3 months (95%CI 15.2–19.3 months) in favor of the combination arm; this study was not powered for this endpoint.

In patients who have experienced significant toxicities attributable to the non-platin agent therapy (e.g. hypersensitivity reaction, neuropathy, profound myelosuppression), single agent platinum therapy with carboplatinum or cisplatin is preferable. If the toxicity is based on the platinum agent, then treatment with gemcitabine, liposomal doxorubicin or taxanes should be considered.

The principles specific to platinum resistant disease are that whenever clinical trials are available, all patients should be offered participation in these trials. In a setting where clinical trials are not available or not appropriate, there are many treatment options which have shown modest response rate but their benefit over best supportive care has not been studied in clinical trials. Drugs with proven efficacy in this setting include etoposide [19–21], gemcitabine [22–25], liposomal doxorubicin [26–28], taxanes [29,30], topotecan [31–36], or vinorelbine [37,38].

The principles specific to platinum refractory disease are that whenever clinical trials are available, all patients should be offered participation in these trials. Patients who progress while upon a platin analogue should be switched to another drug (or to symptom management alone).

Recommendation to stop chemotherapy is an option as a patient who is treated with repeated regimens of chemotherapy, may have diminishing benefits in terms of duration and degree of response. There is a single institution Canadian study [39] which has shown that survival is less than 6 months when the length of interval between the two preceding relapses is less than 12 months from the first to second relapse and less than 6 months from the first to third, or second to fourth and so on. Thus, patients and their support network need to be apprised of the situation and the purpose of further interventions. Best supportive care based

on the patient's current presentation (i.e. pain then appropriate pain relief) should always be an option.

The panel is aware of two ongoing Phase III trials of relevance to this guideline. The first trial, Caelyx plus carboplatin versus paclitaxel plus carboplatin in patients with epithelial cancer in late relapse (Protocol ID EudraCT2004-004456-39, NCT001189553, CALYPSO), is a study of the efficacy and safety of caelyx in combination with carboplatin compared to the standard treatment of paclitaxel and carboplatin in patients with epithelial ovarian cancer in late relapse (>6 months). A second trial, MITO-2: A study comparing 2 chemotherapy regimens (carboplatin/liposomal doxorubicin versus carboplatin/paclitaxel) in patients with ovarian cancer (MITO-2, NCT00326456, EudraCT number 2005-004453-98), is to compare the effectiveness (progression free survival) of the experimental combination of carboplatin and liposomal doxorubicin with the standard combination of carboplatin and paclitaxel in first line treatment of patients with ovarian cancer.

Scheduled review and update

This guideline will be reviewed by the GOC in conjunction with the CSCC CPG-AG no later than 2 years from its date of creation, October 2006, to ensure that the recommendations remain up-to-date. The degree of update, if required, will depend on the interim publication of relevant information (e.g. systematic reviews, health technology assessments, clinical trial data) or any other factors that may affect the recommendations as outlined in this document [9].

Discussion

This guideline on the use of systemic therapy for women with recurrent ovarian cancer represents the first successful interaction between a disease specific society (GOC) and CSCC-CPG-AG. It is the first national approach to developing guidelines on a controversial topic. The strengths of this guideline is that it addresses a specific question. The process included a broad spectrum of stakeholders included clinicians and methodologist. They represented the geographic diversity of Canada and a multidisciplinary clinical perspective. Given the enormous resources involved in creating a guideline, the CSCC-CPG-AG has participated in the development and implementation of tools such the AGREE instrument and the recommendation matrix which allows clinicians to quickly and clearly grasp the methodological quality of prior guidelines and then focuses the discussion on issues related to individual recommendations. Our final national guideline product has received endorsement through the process of practitioner feedback and unanimous approval by the executive of our national society (the GOC). The success of this process bodes well for future collaborations where there is national clinical practice variation.

The limitations of this process is that it reflects the currently approved documents and must currently be updated depending on the results of recently completed trials and assessment of the

peer review publication of these trials. Thus there may be a significant delay between the time where results are presented in the scientific community and when the study can be evaluated in detail from the journal and then vetted through a guideline process. Our document reflects a Canadian socialized medicine context where funding of new and expensive technologies is based on randomized phase 3 trials where overall survival is the end point of interest in contrast to disease free survival or quality of life end points.

How this guideline influences drug access and reimbursement on the national scene was beyond the scope of this endeavor. However, having a clearly identified process and peer review approval documenting its validity and reliability can only infuse confidence and guidance for clinicians in the physician–patient decision making process as well as for policy makers when vetting approval for a myriad of high cost pharmaceutical and technologic interventions currently in the queue for provincial/federal funding. The goal of this guideline is to provide evidence-based guidance for clinicians and women with recurrent ovarian cancer in Canada. The strong support provided in the practitioner feedback bodes well for the implementation of the guideline. Monitoring the future care of women in this circumstance will be required to understand whether knowledge and endorsement result in changes in practice.

Acknowledgments

Funding provided by the Canadian Institute for Health Research, GOC and the CSCC-CPG-AG. Collaborators on the National Clinical Practice Guideline, Laurie Elit, Chair, Gynecologic Oncologist, Juravinski Cancer Centre; Peter Craighead, Radiation Oncologist, Tom Baker Cancer Centre; Lesa Dawson, Gynecologic Oncologist, Newfoundland Cancer Treatment and Research Foundation; Michael Fung Kee Fung, Gynecologic Oncologist, Ottawa Hospital Regional Cancer Centre; Walter Gotlieb, Gynecologic Oncologist, Jewish General Hospital, Québec; Prafull Ghatage, Gynecologic Oncologist, Tom Baker Cancer Centre, Alberta; Robert Lotocki, Gynecologic Oncologist, Cancer Care Manitoba; Dianne Miller, Gynecologic Oncologist, BC Cancer Agency; Joan Murphy, Gynecologic Oncologist, University Health Network, Ontario; Diane Provencher, Gynecologic Oncologist, Hopital Notre Dame, Québec, President of GOC; Barry Rosen, Gynecologic Oncologist, University Health Network Ontario; Réjean Savoie, Gynecologic Oncologist, New Brunswick; Luis Souhami, Radiation Oncologist, Montréal General Hospital, Québec; Gavin Stuart, Gynecologic Oncologist, Dean of Medicine, University of British Columbia; Ken Swenerton, Medical Oncologist, BC Cancer Agency; Melissa Brouwers, Program in Evidence based Care, Cancer Care Ontario; George Browman, Haematologist, CEO Tom Baker Cancer Centre; Ian D. Graham, Health Sociologist, Ottawa Health Research Institute; Louise Zitzelsberger, Research Methodologist, Ottawa Health Research Institute; Louise Paquet, Québec Guidelines Group, Government of Québec; Jill Petrella, Cancer Care Nova Scotia; Susie Lau, Gynecologic Oncologist, Jewish General Hospital, Montréal, Quebec.

Appendix A. Strength of the recommendation and levels of evidence

Rating	Definition
<i>Scale for strength of recommendation</i>	
A	Good evidence for efficacy and substantial clinical benefit support recommendation for use
B	Moderate evidence for efficacy or only limited clinical benefit support recommendation for use
C	Evidence for efficacy is insufficient to support a recommendation for or against use, but recommendations may be made on other grounds
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use
<i>Scale for quality of evidence</i>	
I	Evidence from at least 1 randomized controlled trial
II	Evidence from at least 1 clinical trial without randomization, from cohort or case-controlled analytic studies, or from multiple time series studies or dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

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