ORIGINAL ARTICLES

Chemotherapy for recurrent epithelial ovarian cancer previously treated with platinum - a systematic review of the evidence from randomized trials

M. Fung Kee Fung[1], *MB BS FRCS(C)*; **M. E. Johnston**[2], *BSc*; **E. A. Eisenhauer**[3], *M.D. FRCP(C)*; **L. Elit**[4], *M.D. MSc FRCS(C)*; **H. W Hirte**[5], *M.D. FRCP(C)*; **B. Rosen**[6], *M.D. FRCS(C)*

On behalf of the Cancer Care Ontario Practice Guidelines Initiative Gynecology Disease Site Group
[1]Department of Obstetrics and Gynaecology, University of Ottawa, Ottowa, ON
Head, Division of Surgical Oncology, Ottawa Regional Cancer Centre, Ottawa ON
Chair, Gynecology Disease Site Group, Cancer Care Ontario Practice Guidelines Initiative
[2]Research Assistant, Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton ON
[3]Director, Investigational New Drug Program, National Cancer Institute of Canada Clinical Trials Group;
Professor, Department of Oncology, Queen's University; Kingston ON
[4]Gynecologic Oncologist, Division of Gynecologic Oncology, Hamilton Regional Cancer Centre;
Assistant Professor, Department of Obstetrics & Gynecology, McMaster University; Hamilton ON
[5]Head of Medical Oncology, Hamilton Regional Cancer Centre;
Associate Professor, Departments of Medicine and Obstetrics & Gynecology, McMaster University; Hamilton ON
[6]Associate Professor , Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Toronto, Toronto ON (Canada)

Summary

Purpose: To evaluate the chemotherapeutic options for women with recurrent epithelial ovarian cancer who have received platinum-based chemotherapy.

Methods: A systematic search of the Medline, CancerLit and Cochrane Library databases was performed for the period from 1984 to June 2001 to find randomized trials comparing second- or higher-line chemotherapy regimens in patients with recurrent platinum-pretreated epithelial ovarian cancer.

Results: Seven randomized trials have failed to demonstrate the clear superiority of any one chemotherapy regimen in terms of improvements in long-term survival, quality of life or response rate. One trial detected a statistically significant difference between treatments in progression-free survival, which was longer with cyclophosphamide/doxorubicin/cisplatin than with paclitaxel in women with platinum-sensitive ovarian cancer. Another trial did not show a difference between liposomal doxorubicin and topotecan overall in women with recurrent ovarian cancer but a subgroup analysis detected a significant survival advantage for liposomal doxorubicin over topotecan in women with platinum-sensitive disease.

Conclusion: The evidence available does not support firm conclusions about the preferred chemotherapy regimen for recurrent ovarian cancer. Randomized trials that compare new drugs with current standard treatments are needed.

Key words: Ovarian cancer, Recurrent, Chemotherapy, Platinum

Introduction

Ovarian cancer represents a significant cause of morbidity and mortality in women. In Canada, in 1997 an estimated 25,000 years of life were lost making it the fourth leading cause of cancer death in women [1].

Currently, standard primary therapy for advanced disease generally involves the combination of maximal cytoreductive surgery and chemotherapy with platinum (cisplatin or carboplatin) plus paclitaxel. In spite of initial high response rates, a large proportion of patients will relapse [2], resulting in a therapeutic challenge. Because these patients are not curable [3], the goal of therapy becomes improvement in both the quality and length of life. There is some evidence to suggest that the palliative use of chemotherapy can improve the quality of life in this setting and may even be cost effective [4], but no randomized studies have compared chemotherapy to best supportive care. In spite of the issues surrounding the treatment of patients with recurrent ovarian cancer, there is a growing willingness among patients to undergo aggressive therapies for modest gains in response rates, as has been documented in some other disease sites [5]. This has added a further dimension to the question of the optimal treatment choice in this setting. The search, therefore, has been to find agents or combination regimens for women with recurrent disease following platinum-based chemotherapy which are active in producing regression of tumour, improvement in symptoms and increases in survival.

At present, there are a number of standard and novel medications available but their relative merits are difficult to assess. Few randomized trials have been conducted and even fewer prospective trials have directly evaluated the impact of treatment on quality of life. There

Revised manuscript accepted for publication December 10, 2001

are, however, tumour response data available from a large number of phase II studies [6]. Indirect comparisons among the agents assessed in these single-arm trials is complicated by the different methods used for classifying responsiveness to treatment. One of the most frequently documented clinical surrogates for predicting response to chemotherapy in this setting has been the platinum-free interval (i.e., the period of time from primary platinum-based chemotherapy to recurrence). Responsiveness, described in terms of platinum resistance or sensitivity, is best characterized as a continuum. Increasing sensitivity to platinum is positively correlated with time from the completion of initial treatment to recurrence, such that patients who recur beyond two years after the end of primary therapy have response rates to retreatment with platinum approaching those for primary therapy [7].

Women with platinum-resistant disease, defined as those who relapse within six months of completion of primary therapy, have uniformly low response rates to therapy. Further complicating the decision of what to offer these patients is the wide range of approaches to treatment among specialists dealing with this dilemma. The options range from therapy for symptomatic disease, using less toxic treatments including single-agent chemotherapy as well as best supportive care, to aggressive therapy for asymptomatic patients, using a range of multi-agent regimens. In addition, recent phase I and II trials have demonstrated activity in this setting for a number of new and emerging drugs, which has added to the confusion about which of many treatment options is optimal, balancing efficacy and toxicity [8-16].

To evaluate the therapeutic options available, we have undertaken a systematic review of the published literature with a view to identifying the evidence from randomized trials on the efficacy of single- and multiple-agent systemic therapy in this setting. We were primarily interested in evidence that would support recommendations for therapy on the basis of improved survival or improvement in quality of life/symptom palliation. Since many trials fail to document symptom palliation as an important endpoint, we explored response rate and time to progression as surrogates for this measure.

Methods

Literature search strategy

The Medline, CancerLit and Cochrane Library databases were searched for literature published between 1984 and June 2001, using the MeSH terms 'antineoplastic agents', 'ovarian neoplasms/dt' and 'neoplasm recurrence, local', and the text words 'chemotherapy', 'platinum', 'pretreated', 'resistant', 'resistance', 'recurrent', 'recurrence', 'relapse', 'ovarian', 'ovary', 'neoplasm', 'cancer' and 'carcinoma'. Methodologic terms related to randomized trials were also used. The reference lists of papers and review articles identified by these sources, and the proceedings of the recent (1997-2001) meetings of the American Society of Clinical Oncology (ASCO) were scanned for additional citations. Searches were restricted to English-language publications.

Inclusion criteria

Articles (either full papers or abstracts) were eligible for inclusion in this systematic review if they mert all of the following criteria:

1. The paper described a randomized controlled trial (RCT).
2. The study included patients with recurrent epithelial ovarian cancer who had been previously treated with platinum.
3. Patients in the trial were classified according to platinum resistance. Where both platinum-resistant and platinum-sensitive patients were included, results for at least one outcome were presented separately for these two groups.
4. Systemic chemotherapy was administered as second-, third- or higher-line treatment for ovarian cancer.
5. The report included survival, tumour-response, time-to-progression or quality-of-life data.

Exclusion criteria

1. Studies that evaluated intraperitoneal chemotherapy or the use of chemotherapy with bone marrow or stem cell transplantation were excluded.
2. Studies that evaluated hormonal therapy for recurrent ovarian cancer were excluded.

Synthesizing the evidence

Data from the randomized trials were not pooled quantitatively because the trials evaluated different treatment regimens.

Results

Ten randomized trials were found by the search [17-26]. Three of these were did not clearly describe the platinum-resistance status of participants and were therefore ineligible for inclusion in this systematic review [17-19]. Each of the three studies compared different schedules for a single agent.

Seven of the ten trials met the eligibility criteria described above [20-27]; these trials are listed in Table 1. Two studies were labelled as randomized phase II trials [21, 24]. A trial of paclitaxel versus topotecan was described in a published paper by ten Bokkel Huinink *et al.* in 1997 [22] and final results were subsequently presented in a meeting abstract in 1998 by Gordon *et al.* [23]; data related to survival, time to progression and quality of life from the abstract are included in this systematic review.

Five RCTs have been published in full and included detailed descriptions of eligibility criteria [20, 22, 24-26]; all were restricted to women with Eastern Cooperative Oncology Group (ECOG) or World Health Organization (WHO) performance status of 2 or less, or a Karnofsky performance status ≥ 60%. Five studies were restricted to women who had received one previous course of chemotherapy [20, 22, 25-27]. Sixty-nine percent of patients in the trial of paclitaxel versus oxaliplatin by Piccart *et al.* had received one prior chemotherapy regimen and 31% two regimens [24]. Only patients who had not received previous treatment with paclitaxel were eligible for the trials by ten Bokkel Huinink *et al.*, Bolis *et al.* and Piccart *et al.* [22, 24, 26].

None of the trials were blinded. Three used an intention-to-treat approach to analysis [20, 22, 26]. Four trial reports described an appropriate method for concealing allocation up to the time of randomization [20, 22, 24, 26] and two described the number of patients lost to follow-up [20, 22].

The Colombo trial and one of the Bolis trials were restricted to platinum-sensitive cases [20, 21]; Bolis *et al.*

Table 1. — *Randomized trials of chemotherapy for recurrent, platinum-pretreated ovarian cancer*

Study	Treatment groups	Prior chemotherapy -# regimens (% of patients)	#platinum-sensitive patients	#platinum-resistant patients	Median duration of follow-up (months)
Bolis, 2001 [20]	carboplatin vs carboplatin+epirubicin	one	191	–	not reported
Colombo, 1996 [21] (randomized phase II trial, abstract)	paclitaxel vs cyclophosphamide +doxorubicin+cisplatin	not reported	79	–	17
ten Bokkel Huinink, 1997 [22, 23]	paclitaxel vs topotecan	one	107	119	not reported
Piccart, 2000 [24] (randomized phase II trial)	paclitaxel vs oxaliplatin	one (69%) or two (31%)	23	63	not reported
Gordon, 2001 [25]	topotecan vs liposomal doxorubicin	one	220	254	not reported
Bolis, 1999 [26]	paclitaxel vs paclitaxel+epirubicin	one	–	81	10
Torri, 2000 [27] (abstract)	paclitaxel vs paclitaxel+doxorubicin	one	–	196	24

Table 2. — *Survival data from randomized trials of chemotherapy for recurrent, platinum pretreated ovarian cancer*

Study	Treatment groups	Median survival (months)	
		Platinum-sensitive	Platinum-resistant
Bolis, 2001 [20]	carboplatin 300 mg/m² (n=95) carboplatin 300 mg/m²+epirubicin, 120 mg/m² (n = 95)	23.5 27.5 p = NS	–
Colombo, 1996 [21] (randomized phase II trial, abstract)	paclitaxel 175 mg/m², 3-hour infusion (n = 41) CAP (n = 38): cyclophosphamide, 500 mg/m²+doxorubicin, 50 mg/m² +cisplatin, 50 mg/m²	20.3 24.3 p = 0.873	–
ten Bokkel Huinink, 1997 [23]	paclitaxel, 175 mg/m², 3-hour infusion (n = 114) topotecan, 1.5 mg/m², 30-minute infusion (n = 112)	13.3 15.8 p = 0.872	
Piccart, 2000 [24] (randomized phase II trial)	paclitaxel, 175 mg/m², 3-hour infusion (n = 41) oxaliplatin, 130 mg/m² (n = 45)	9.3 10.5 p-value not reported, analyzed as 2 parallel phase II trials	
Gordon, 2001 [25]	topotecan, 1.5 mg/m², 30 minute infusion (n = 111 sensitive + 124 resistant) liposomal doxorubicin, 50 mg/m² (n = 109+130)	16.4 24.9 p = 0.008	9.5 8.2 p = 0.455
Bolis, 1999 [26]	paclitaxel, 175 mg/m², 3-hour infusion (n = 41) paclitaxel, 150 mg/m², 3-hour infusion; +epirubicin, 120 mg/m² (n = 40)	–	2-year survival rates: 18% 10% p = 0.33
Torri, 2000 [27] (abstract)	paclitaxel, 175 mg/m², 3-hour infusion (n = 90) paclitaxel, 175 mg/m², 3-hour infusion; + doxorubicin, 80 mg/m² (n = 96)		14 12 p = 0.39

NS = not statistically significant.

used a cut-off of six months since last platinum treatment as the definition of sensitive disease and Colombo *et al.* a 12-month cut-off. In the trials by ten Bokkel Huinink *et al.* [22] and Gordon *et al.* [25], platinum-sensitivity was defined as a complete or partial response to platinum-based chemotherapy followed by relapse more than six months after chemotherapy was stopped. Just under half of the patients participating in these trials were platinum-sensitive, and tumour response rates were presented separately for this subgroup and the platinum-resistant cases. The platinum-sensitive stratum in the trial by Piccart *et al.* made up 27% of the study population and had platinum-free intervals ranging from six to 12 months [24]. A second trial by Bolis *et al.* was restricted to platinum-resistant cases [26]; platinum resistance was defined as no response to initial chemotherapy, a complete or partial response followed by progression while still on therapy, or a response to platinum-based chemotherapy followed by relapse less than six months after chemotherapy was stopped. The trial by Torri *et al.*, reported only in abstract form, was restricted to women with progressive disease within 12 months from the end of first-line platinum-based treatment [27].

Survival data are reported in Table 2. Although the studies by ten Bokkel Huinink *et al.* [22, 23] and Piccart *et al.* [24] included both platinum-sensitive and platinum-resistant patients, survival results were not given separately for these groups. In the studies by ten Bokkel Huinink *et al.* [22, 23] and Colombo *et al.* [21], patients who failed to respond to one regimen could cross over to the other treatment. In the former trial, 54% of the patients randomized to paclitaxel received topotecan after failing to respond to paclitaxel, and 44% of the topotecan group received paclitaxel [23]. Nineteen of 41 patients (46%) allocated to paclitaxel in the trial by Colombo *et al.* crossed over to cyclophosphamide/doxorubicin/cisplatin (CAP) after failing paclitaxel, while 12 of 38 patients (32%) in the CAP arm received paclitaxel [21].

Overall, there were no significant differences in survival between treatment regimens assessed in these trials. Gordon *et al.* detected no survival difference between liposomal doxorubicin and topotecan in women with recurrent ovarian cancer (median survival times for all patients (i.e., platinum-sensitive or -resistant) were 13.1 months with topotecan (n = 235) and 13.8 months with liposomal doxorubicin (n = 239)) but a subgroup analysis found a significant survival advantage for liposomal doxorubicin over topotecan in women with platinum-sensitive disease [25].

Three randomized trials assessed quality of life (QoL) during chemotherapy for recurrent ovarian cancer [22, 24, 25]. All used the European Organization for Research and Treatment of Cancer (EORTC) QLQ-30 questionnaire to measure symptoms at baseline and during chemotherapy. Gordon *et al.* reported, in an abstract prepared for the 1998 ASCO meeting [23], that there were no statistically significant differences between topotecan and paclitaxel in measures of pain, anorexia, diarrhea, fatigue, nausea and vomiting, dyspnea, constipation, and insomnia during the randomized trial originally reported

Table 3. — *Response data from randomized trials of chemotherapy for recurrent, platinum pretreated ovarian cancer*

Study	Treatment groups	Response rate (complete + partial)		Median time to progression (weeks)	
		Platinum=sensitive	Platinum-resistant	Platinum-sensitive	Platinum-resistant
				Progression-free survival:	
Bolis, 2001 [20]	carboplatin	55%	–	14.7	–
	carboplatin+epirubicin	58%	–	18.7	–
		p = 0.670*		p = NS	
				Progression-free survival:	
Colombo, 1996 [21]	paclitaxel	49%	–	29.2	–
(randomized phase II trial,	CAP	54%	–	75.6	–
abstract)				p = 0.014	
ten Bokkel Huinink,	paclitaxel	20%	7%	14.7	
1997 [22, 23]	topotecan	29%	13%	18.9	
		p = 0.213	p = 0.303	p = 0.072	
Piccart, 2000 [24]	paclitaxel	20%	16%	14	
(randomized phase II trial)	oxaliplatin	38%	6%	12	
				p-value not reported	
				Progression-free survival:	Progression-free survival:
Gordon, 2001 [25]	topotecan	29%	7%	23.3	13.6
	liposomal doxorubicin	28%	12%	28.9%	9.1
		p = 0.964	p = 0.118	p = 0.037	p = 0.733
Bolis, 1999 [26]					Duration of response:
	paclitaxel	–	17%	–	24
	paclitaxel+epirubicin	–	34%	–	40
			p = 0.10		p-value not reported
Torri, 2000 [27]	paclitaxel	–	54%	–	7.5
(abstract)	paclitaxel+doxorubicin	–	52%	–	6.6
			p = 0.747*		p = NS

CAP: cycolophospamide + doxorubicin + cisplatin, *reviewer's calculation.

Table 4. — *Percentage of patients with grade 3 or 4 adverse effects in randomized trials of chemotherapy for platinum-pretreated ovarian cancer*

Study	Treatment groups	Grade 3/4 Neutropenia	Grade 3/4 Thrombocytopenia	Grade3/4 Anemia	Grade3/4 Nausea & Vomiting	Grade3/4 Neurotoxity
Bolis, 2001 [20]	carboplatin	13%	20%	10%	3%	
	vs					not reported
	carboplatin+epirubicin	53%	64%	25%	13%	
Colombo, 1996 [21]	paclitaxel	12%			10%	(Grade 2-3)
	vs		not reported	not reported		not reported
	CAP	42%			34% (Grade 2-3)	
ten Bokkel Huinink, 1997 [22]	paclitaxel	52%	3%	6%	3%	0%
	vs					
	topotecan	95%	50%	41%	10%	0%
Piccart, 2000 [24]	paclitaxel	22%	0	2%	2%	7%
	vs					
	oxaliplatin	0	4%	2%	7%	9%
Gordon, 2001 [25]	topotecan	77%	34%	28%		
	vs				not reported	not reported
	liposomal doxorubicin	12%	1%	5%		
Bolis, 1999 [26]	paclitaxel	24%	2%	12%	2%	0%
	vs					
	paclitaxel+epirubicin	45%	25%	30%	8%	3%
Torri, 2000 [27] (abstract)	paclitaxel	7%				
	vs		not reported	not reported	not reported	not reported
	paclitaxel+doxorubicin	24%				

CAP: cycolophospamide + doxorubicin + cisplatin.

by ten Bokkel Huinink *et al.* [22]. Among the participants who completed the quality-of-life questionnaire after four cycles of treatment in the trial by Piccart *et al.* (47%), the mean QoL score increased by an average of more than 10 points from baseline values in the paclitaxel group and was unchanged in the oxaliplatin group [24]. Gordon *et al.* reported that there were no significant differences between the topotecan and liposomal doxorubicin groups in any measure of quality of life 12 weeks after starting chemotherapy, but did not present any detailed results [25].

Because very few data on quality of life and symptom control have been reported in the literature, we have used tumour response and time to progression (progression-free interval) as surrogates for palliation (Table 3). Time to progression was reported for all seven randomized trials. Colombo *et al.* reported that progression-free survival was longer with cyclophosphamide/doxorubicin/-cisplatin than with paclitaxel (76 vs 29 weeks, p = 0.014) in women with platinum-sensitive ovarian cancer [21]. Median time to progression for all patients (i.e., platinum-sensitive or -resistant) in the trial by Gordon *et al.* was 17.0 weeks with topotecan (n = 235) and 16.1 weeks with liposomal doxorubicin (n = 239) [25].

Five randomized trials have reported tumour response rates from direct comparisons of chemotherapeutic options for the treatment of platinum-sensitive recurrent ovarian cancer [20-25] and five have presented response rates for the treatment of platinum-resistant recurrent ovarian cancer [22-27]. Three trials that included both platinum-resistant and -sensitive disease detected higher response rates among platinum-sensitive patients compared with platinum-resistant patients [22-25]. However, none of the RCTs demonstrated statistically significant differences in tumour response rates between treatment groups (Table 3).

Toxicity data from randomized trials are summarized in Table 4. The trials by ten Bokkel Huinink *et al.* [22], Piccart *et al.* [24] and Gordon *et al.* [25] used the National Cancer Institute common toxicity criteria, while Bolis *et al.* [20, 26] and Torri *et al.* [27] used the World Health Organization grading system. The abstract report of the Colombo trial did not describe the grading systems used [21]. There were two treatment-related deaths attributed to sepsis in the topotecan group in the trial by ten Bokkel Huinink *et al.* [22] and four in the Gordon trial [25]. Sepsis was reported for 6% of patients on topotecan, 1% on paclitaxel and none on liposomal doxorubicin. Twenty-five percent of the women treated with liposomal doxorubicin experienced grade 3 or 4 palmar-plantar erythrodysthesia and four patients (3%) discontinued treatment because of this adverse effect of treatment [25].

Discussion

Two key concepts need to be kept in mind when interpreting the evidence related to chemotherapy for recurrent or relapsed ovarian cancer.

1. The goals of therapy are to improve quality of life and extend survival. In light of this, therapies need to be assessed on the basis of sound risk/benefit ratios, as well as documented improvements in quality of life and performance status. Because these data are sparse, tumour response rate (the most commonly reported study outcome) has been used as a surrogate outcome. While this is not ideal, there is empirical evidence that it is a reasonable and useful surrogate for survival in ovarian

cancer. du Bois *et al.* showed a positive correlation ($p < 0.0001$ for platinum-sensitive disease and $p = 0.0069$ for platinum-refractory disease) between response and survival rates from individual phase II studies of treatments for platinum-pretreated ovarian cancer [6]. Regimens that are less toxic and simple to administer may contribute to enhanced quality of life. Furthermore, at least in a breast cancer setting, there is evidence to suggest patients who have an objective tumour response have a higher probability of experiencing improvement in disease related symptoms [28]. If recurrent ovarian cancer symptoms may at least in part be due to tumour bulk, it is intuitively reasonable that substantial shrinkage in that bulk (as is the case to meet criteria for complete or partial responses) would coincide with symptom improvement as well. We acknowledge this is not an ideal surrogate but in the absence of information about symptom change in many studies, it is a defensible one.

2. The identification of subgroups of patients who would benefit preferentially from treatment is needed. One of the most useful clinical predictors for survival has been whether the disease is platinum-sensitive or platinum-resistant. Patients with tumours that are platinum-sensitive respond to re-induction with platinum chemotherapy, with response rates of 30-40% [29]. Response rates are even higher if more than two years have elapsed since primary therapy [30]. This is in contrast to patients with platinum-resistant tumours, that show response rates of less than 10% [31]. In view of the clinical utility of this marker (sensitivity/resistance to platinum), there is a need to interpret the evidence from clinical trials in this context. It is only recently that reports of trials have defined patient populations in terms of platinum sensitivity and resistance, allowing for some comparison among trials.

Adding to the challenge of interpreting the evidence on chemotherapy for recurrent ovarian cancer is the small number of comparative studies, especially phase III trials, that have been conducted. At present there is evidence from seven randomized trials in platinum pretreated patients [20-27]. While one study detected a significant survival advantage for liposomal doxorubicin over topotecan in a subgroup analysis [25], the other six trials detected no difference between treatments with respect to the duration of survival. One randomized phase II trial detected a significantly longer median time to progression with cyclophosphamide/doxorubicin/cisplatin compared to paclitaxel in platinum-sensitive disease [21]. None of the RCTs demonstrated statistically significant differences in tumour response rates between treatment groups. Of three trials that evaluated quality of life [23-25], one did not detect a difference between paclitaxel and topotecan [22]; the second, a randomized phase II trial, found that paclitaxel improved quality of life scores while oxaliplatin did not [24]; and the third concluded that there were no significant differences between topotecan and liposomal doxorubicin [25].

No evidence is available on retreatment with platinum monotherapy versus combination therapy (e.g., platinum plus paclitaxel) in the subset of patients with platinum-free intervals exceeding two years who would be expected to have response rates approaching those for primary therapy.

There is a large body of data available from single-arm phase II trials, which has been summarized in a comprehensive systematic review by du Bois *et al.* [6]. When data from phase II studies were pooled, several drugs provided response rates greater than 20% in platinum-sensitive disease; these included platinum and platinum-based combinations, paclitaxel and etoposide. In platinum-sensitive disease, retreatment with a platinum compound produced high response rates even when compared indirectly to a novel agent such as topotecan. In platinum-resistant disease, response rates observed in phase II trials are often less than 20%, but drugs with pooled response rates greater than 20% in the du Bois systematic review included etoposide, docetaxel and gemcitabine. However, not all of these agents have been evaluated in randomized trials in this setting.

Randomized trials that compare new drugs with current standard treatments should be the model for future research in this area. In addition to the traditional outcomes of survival and time to progression, clinical trials should examine the impact of treatment on overall quality of life, as well as measurement of symptom palliation, and should provide data on the relative costs of treatments. If possible, future research should evaluate drugs that are not cross-resistant to platinum and paclitaxel, although such agents seem elusive to date. It has been hypothesized that second-line chemotherapy with non-platinum agents may extend the platinum-free interval and thereby maximize response to subsequent treatment with platinum [30,32]. It has also been suggested that second-line therapy with platinum prior to other agents may promote drug resistance and reduce the likelihood of response to subsequent chemotherapy. The early use of non-platinum agents in recurrent ovarian cancer should be investigated in randomized trials that assess survival, quality of life and toxicity.

Conclusion

There have been only a few phase III trials comparing chemotherapy options for this patient population, and there is no evidence of the clear superiority of any one regimen over others in terms of improvements in long-term survival, quality of life or response rate. Women with recurrent ovarian cancer who have received previous treatment with platinum should participate in randomized clinical trials.

Based on the existing evidence, treatment options should be considered in the context of whether the patient's tumour is platinum sensitive or resistant. In choosing medication, consideration should be given to non-cumulative toxicity. For women with platinum-sensitive disease (recurrence more than six months after primary chemotherapy) who do not participate in clinical trials, the re-introduction of platinum monotherapy (carboplatin) is the preferred option. Carboplatin produces tumour response rates similar to those for other agents

but has lower toxicity and is easier to administer. For women with platinum-sensitive disease who have an allergy to carboplatin or who have experienced significant adverse effects from carboplatin, treatment with non-platinum-agents that have been evaluated in randomized clinical trials (such as topotecan, paclitaxel or liposomal doxorubicin) may be considered. Topotecan, paclitaxel or liposomal doxorubicin are also treatment options for women with platinum-resistant recurrent ovarian cancer who do not participate in clinical trials.

References

[1] National Cancer Institute of Canada: Canadian Cancer Statistics 2001, Toronto, Canada, 2001.

[2] McGuire W. P., Ozols R. F.: "Chemotherapy of advanced ovarian cancer". *Semin. Oncol.* 1998, *25 (3)*, 340.

[3] Ozols R. F. "Treatment of recurrent ovarian cancer: Increasing options - "recurrent" results [editorial].": *J Clin. Oncol.* 1997, *15 (6)*, 2177.

[4] Patnaik A, Doyle C, Oza A. M.: "Palliative therapy in advanced ovarian cancer: balancing patient expectations, quality of life and cost". *Anti-Cancer Drugs* 1998, *9 (10)*, 869.

[5] Slevin M. L., Stubbs L, Plant H. J., Wilson P, Gregory W. M., Armes P. J. *et al.*: "Attitudes to chemotherapy: comparing views of doctors, nurses, and general public". *Br. Med. J.*, 1990, *300 (6737)*, 1458.

[6] du Bois A., Luck H. J., Meerpohl H. G.: "Treatment for recurrent or progressive ovarian cancer failing first-line chemotherapy: a review of systemic treatment modalities". *Zentralbl. Gynakol.*, 1997, *119 (7)*, 299.

[7] Gore M. E., Fryatt I., Wilthsaw E., Dawson T:. "Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds". *Gynecol. Oncol.*, 1990, *36 (2)*, 207.

[8] Markman M., Blessing J., Alvarez R. D., Hanjani P., Waggoner S., Hall K.: "Phase II evaluation of 24-h continuous infusion topotecan in recurrent, potentially platinum-sensitive ovarian cancer: a gynecologic oncology group study". *Gynecol. Oncol.*, 2000, *77 (1)*, 112.

[9] McGuire W. P., Blessing J. A., Bookman M. A., Lentz S., Dunton C. J.: "Topotecan has substantial antitumor activity as first-line salvage therapy in platinum-sensitive epithelial ovarian carcinoma: a gynecologic oncology group study". *J. Clin. Oncol.*, 2000, *18 (5)*, 1062.

[10] Bustova I., Blaha O., Brychta M., Janousek M., Kalabova R., Hanus L., *et al.*: "Topotecan in the treatment of advanced recurrent epithelial ovarian cancer [abstract]". *Proc. Am. Soc. Clin. Oncol.*, 2000, *19*, 397a.

[11] Kaufmann M., von Minckwitz G. "Gemcitabine in ovarian cancer: an overview of safety and efficacy". *Eur .J. Cancer*, 1997, *33(Suppl. 1)*, S31.

[12] Coenen M., Berteloot P., Amant F., Vangramberen M., Vergote I.: "Gemcitabine in platin-paclitaxel resistant ovarian carcinoma [abstract]". *Proc. Am. Soc. Clin. Oncol.*, 2000, *19*, 405a.

[13] von Minckwitz G., Bauknecht T., Vissern-Grul C. M., Neijt J. P.: "Phase II study of gemcitabine in ovarian cancer". *Ann. Oncol.*: 1999, *10 (7)*, 853.

[14] Muggia F. M., Hainsworth J. D., Jeffers S., Miller P., Groshen S., Tan M. *et al.*: "Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation". *J. Clin. Oncol.*, 1997, *15(3)*, 987.

[15] Medi-View Express Report.: "The promise of targeted novel chemotherapy in solid tumors". *Proceedings of the10th Biennial European Cancer Conference (ECCO 10)*, 1999 Sept 12-16, Vienna, Austria.

[16] Gordon A. N., Granai C. O., Rose P. G., Hainsworth J., Lopez A., Weissman C. *et al.*: "Phase II study of liposomal doxorubicin in platinum- and paclitaxel-refractory epithelial ovarian cancer". *J. Clin. Oncol.*, 2000; *18 (17)*, 3093.

[17] Eisenhauer E., ten Bokkel Huinink W. W., Swenerton K. D., Gianni L., Myles J., van der Burg M. E. *et al.*: "European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose versus low-dose and long versus short infusion". *J. Clin. Oncol.*, 1994, *12 (12)*, 2654.

[18] Hoskins P., Eisenhauer E., Beare S., Roy M., Drouin P., Stuart G. *et al.*: "Randomized phase II study of two schedules on topotecan in previously treated patients with ovarian cancer: a National Cancer Institute of Canada Clinical Trials Group study". *J. Clin. Oncol.*, 1998, *16 (6)*, 2233.

[19] Sugiyama T., Nishida T., Ookura N., Yakushiji M., Ikeda M., Noda K *et al.*: "Is CPT-11 useful as a salvage chemotherapy for recurrent ovarian cancer? [abstract]". *Proc. Am. Soc. Clin. Oncol.*, 1997, *16*, 378a.

[20] Bolis G., Scarfone G., Giardina G., Villa A., Mangili G., Melpigano M *et al.*: "Carboplatin alone vs carboplatin plus epidoxorubicin as second-line chemotherapy for cisplatin- or carboplatin-sensitive ovarian cancer". *Gynecol. Oncol.*, 2001, *81 (1)*, 3.

[21] Colombo M., Marzola M., Parma G., Cantu M. G., Tarantino G., Fornara G *et al.*: "Paclitaxel vs cap (cyclophosphamide, adriamycin, cisplatin) in recurrent platinum sensitive ovarian cancer: a randomized phase II study [abstract]". *Proc. Am. Soc. Clin. Oncol.*, 1996, *15*, 279.

[22] ten Bokkel Huinink B. W., Gore M., Carmichael J., Gordon A., Malfetano J., Hudson I *et al.*: "Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer". *J. Clin. Oncol.*, 1997, *15 (6)*, 2183.

[23] Gordon A., Carmichael J., Malfetano M., Gore M., Spaczynski M., Clarke-Pearson D *et al.*: "Final analysis of a phase III study of topotecan vs paclitaxel in advanced epithelial ovarian carcinoma [abstract]". *Proc. Am. Soc. Clin. Oncol.*, 1998, *17*, 356a.

[24] Piccart M. J., Green J. A., Lacave A. J., Reed N., Vergote I., Benedetti-Pancini P. *et al.*: "Oxaliplatin or paclitaxel in patients with platinum-pretreated advanced ovarian cancer: a randomized phase II study of the European Organization for Research and Treatment of Cancer Gynecology Group". *J. Clin. Oncol.*, 2000, *18 (6)*, 1193.

[25] Gordon A. N., Fleagle J. T., Guthrie D., Parkin D. E., Gore M. E., Lacave A. J.: "Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan". *J. Clin. Oncol.*, 2001, *19 (14)*, 3312.

[26] Bolis G., Parazzini F., Scarfone G., Villa A., Amoroso M., Rabaiotti E. *et al.*: "Paclitaxel vs epidoxorubicin plus paclitaxel as second-line therapy for platinum-refractory and -resistant ovarian cancer". *Gynecol. Oncol.*, 1999, *72 (1)*, 60.

[27] Torri V., Floriani I., Tinazzi A., Conte P. F., Ravaioli A., Maria Cantù G. *et al.*: "Randomized trial comparing paclitaxel+doxorubicin versus paclitaxel as second line therapy for advanced ovarian cancer patients in early progression after platinum based chemotherapy [abstract]". *Proc. Am. Soc. Clin. Oncol.*, 2000, *19*, 381a.

[28] Geels P., Eisenhauer E., Bezjak A. N., Zee B., Day A.: "The palliative effect of chemotherapy: objective tumor response correlates with symptom improvement in patients with metastatic breast cancer". *J. Clin. Oncol.*, 2000, *18 (12)*, 2395.

[29] Markman M., Rothman R., Hakes T., Reichman B., Hoskins W., Rubin S., Jones: "Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin". *J. Clin. Oncol.*, 1991, *9 (3)*, 389.

[30] Bookman M. A.: "Extending the platinum-free interval in recurrent ovarian cancer: the role of topotecan in second-line chemotherapy". *Oncologist*, 1999, *4 (2)*, 87.

[31] Blackledge G., Lawton F., Redman C., Kelly K.: "Response of patients in phase II studies of chemotherapy in ovarian cancer: implications for patient treatment and design of phase II trials". *Br. J. Cancer*, 1989, *59 (4)*, 650.

[32] Kavanagh J., Tresukosol D., Edwards C., Freedman R., Gonzalez de Leon C., Fishman A. *et al.*: "Carboplatin reinduction after taxane in patients with platinum-refractory epithelial ovarian cancer". *J. Clin. Oncol.*, 1995, *13 (7)*, 1584.

Address reprint requests to:
DR. MICHAEL FUNG KEE FUNG
Ottawa General Hospital
50 Smyth Road,
Ottawa, Ontario K1H 8L6 (Canada)