Treatment of Recurrent Ovarian Cancer

Neville F. Hacker, MD; Michael Friedlander, PhD

Recurrent ovarian cancer is a common clinical problem and the management of each patient must be individualized. Diagnosis is usually based on a progressively rising CA-125 titre, and a CT scan of the pelvis and abdomen, together with a chest X-ray should be performed. Although there is no study to support immediate treatment in the asymptomatic patient, our approach is to commence such patients on Tamoxifen. Chemotherapy is reserved for asymptomatic patients or those who progress on Tamoxifen. The longer the treatment-free interval of 18-24 months. The choice of non-platinum second or subsequent line chemotherapy is based on many factors including likelihood of benefit, potential toxicity, schedule and convenience to the patient, as well as organ function and residual toxicity from prior treatment. Aggressive secondary cytoreductive surgery can significantly prolong survival in those with a disease-free interval of 24 months or more and in those in whom all macroscopic disease can be removed. Radiation therapy to the tumour bed following resection of localized disease may be beneficial in selected patients. Quality of life issues are particularly important for this group of patients and have not been adequately studies. Communication regarding the objectives of therapy is important, and the multidisciplinary approach should include palliative care and psycho-social support, in addition to the more traditional medical options. *(Chang Gung Med J 2004;27:570-7)*

Key words: recurrent ovarian cancer, platinum-free interval, secondary cytoreductive surgery.

Management of patients with recurrent ovarian cancer is a common clinical problem and in general, each patient's treatment must be individualised. There is sufficient literature on the subject to allow some evidence-based decision-making[1,2] but there will inevitably be differences in approach between centres.

The following discussion outlines our approach to recurrent epithelial ovarian cancer at the Royal Hospital for Women in Sydney. We have assumed that the patient is in clinical remission at the completion of 6 cycles of chemotherapy with Carboplatin and Taxol. This article will not address patients presenting with bowel obstruction.

While the majority of women who have late relapses do have recurrent ovarian cancer, there are molecular genetic data to support some patients having new primaries due to field cancerization.[3]

Patient Follow-Up

We follow patients every 3 months for 2 years, every 4 months for one year, every 6 months for 10 years, and at least annually thereafter.

At each visit, a history is taken, and a physical examination, including a pelvic examination, performed.

A CA-125 titre is obtained at each visit, but no x-rays or CT scans are performed routinely. Any suspicious symptoms or physical findings are investi-

From the Department of Gynaecological Cancer Centre, Royal Hospital for Women, University of New South Wales. Randwick, Australia

Address for reprints: Dr. Neville F. Hacker, Department of Gynaecological Cancer Centre, Royal Hospital for Women. University of New South Wales, Randwick, Australia. Tel.: 61+2+93826290 ; Fax: 61+2+93826200; E-mail: N. Hacker@unsw.edu.au

gated appropriately, and a progressively rising CA-125 titre beyond the normal range is investigated with a chest x-ray and CT scan of the pelvis and abdomen.

Management of Rising CA-125 Titres

A common and very controversial issue is how to manage asymptomatic women with a rising CA125 titre and no clinical or radiological evidence of recurrence. The criteria for relapse using CA125 titres vary, but recently there has been some consensus reached, and in the presence of symptoms or signs, CA125 titres have been shown to accurately diagnose disease progression.[4]

Several definitions of progression according to CA125 titres have been proposed. A rise of 50%, 100%, or to levels above the normal range have all been shown to be predictive of relapse, but only one definition has been extensively validated.[5,6] The Gynecologic Cancer Intergroup (GCIG) have proposed that a precise CA125 definition of progression be used as a secondary end point in first-line therapy randomised trials,[7] and they accepted the definition previously validated by Rustin and colleagues.[5] This definition accurately predicts progression in patients whose CA125 level initially falls to normal on first-line treatment and then doubles from the upper limit of normal. In patients whose baseline CA125 level after first-line treatment is not in the normal range, a doubling from the nadir value is also an accurate predictor of progression, with a false-positive rate of < 2% .

The date of progression is defined as either the date of the first doubling of CA125 or the date of progression according to RECIST criteria.[8] If both criteria are met, the first of the two dates is documented as the date of progression. The lead-time between the CA125 titre rising and the patient developing symptoms and / or signs of recurrence is quite variable and ranges from 3-18 months, with a median time of 3 to 4 months. van der Burg et al. reported that a rising CA125 titre has a median lead time of 63 days prior to the date of relapse as identified by standard criteria, and also found that CA125 titres together with routine general and pelvic examinations predicted relapse in 92% of patients, with routine radiological investigations contributing in only 8% of cases.[6]

The MRC/EORTC are addressing the question of whether there is any advantage to starting treatment at the time of CA125 progression, or delaying it until clinical relapse. Until the results are available, the philosophy and approach to management varies considerably.

Our approach is to discuss the findings with the patient, but if clinical examination and radiological investigations are normal as is often the case, we would recommend commencing tamoxifen. We and others have reported complete responses in 11% (0-56%) and prolonged stabilization of CA125 titres in 33% of patients with recurrent ovarian cancer, and this is achieved with little toxicity.[9,10] We would not use tamoxifen in women with ascites or symptoms from large volume recurrent disease. If rising titres persist in spite of Tamoxifen, we would change to chemotherapy.

Treatment of Symptomatic Patients

Patients who relapse 12 months or more following chemotherapy have a good chance of responding to platinum based chemotherapy and the treatment-free interval is often used in determining the choice of chemotherapy. The concept of treatment free interval and its relation to response to platinum was initially described by Blackledge in the late 1980's[11] (Table 1). He noted that patients treated in a phase 2 trial with a treatment free interval of less than 6 months had a response rate of less than 10% whereas those with a treatment-free interval of greater than 18 months had a response rate of 94%. Markman and others subsequently confirmed these findings and the concept of platinum free interval was firmly established.[12,13]

These findings were made at a time when CA125 titres were not routinely used and most patients had clinical or radiological evidence of recurrence and required measurable disease to be treated on phase 2 studies. Whether these same intervals apply to CA125 relapse has, to the best of our knowledge, not been well studied and the same relationship between treatment-free interval and time to CA125 relapse may not hold.

Patients who progress while receiving platinum based chemotherapy are said to have platinum refractory ovarian cancer, and a low likelihood of response to further chemotherapy. Those who relapse within 6

months are considered to have platinum resistant disease but up to 25% of patients will still respond to re-introduction of platinum.Those who relapse greater than 6 months following primary treatment are considered to have potentially platinum sensitive disease.

The longer the duration of response to initial chemotherapy and the longer the treatment free interval, the higher the likelihood of response to re-introduction of platinum, with reported response rates of 65%-94% in patients who have relapsed 18-24 months or more following initial chemotherapy.

The treatment free interval alone is not the only factor that predicts response to second line therapy and Eisenhauer et al defined other variables that predict response.[2] They analyzed 700 patients who participated in clinical trials of paclitaxel,docetaxel or epirubicin and after stepwise logistic regression, only 3 factors independently predicted response. These factors were serous histology, number of disease sites (< 2 vs > 2) and maximum size of largest lesion (< 5 cm vs > 5 cm).The time from last treatment was not an independent prognostic variable as it was highly correlated with tumor size.

There are many potentially active agents available to treat women with recurrent ovarian cancer (Tables 2 and 3). In general we treat all patients who have potentially platinum sensitive disease with carboplatin at relapse, as this is a well tolerated and effective agent as well as being relatively cheap. It does not make any sense to us to withhold carboplatin in patients with potentially "platinum sensitive" disease to increase the platinum free interval, as has been advocated by some authors.[(27)]

We inform all patients about the potential for carboplatin hypersensitivity reactions which may occur after re-introduction of carboplatin.[(30)] This is not usually a problem with first line treatment, but about 10% of women will experience hypersensitivity reactions when carboplatin is re-introduced, typically with the second or third cycle of treatment. The reactions may range from minor degrees of pruritis, to generalised erythema and chest tightness, to anaphylaxis rarely. We have recently described our experience, as well as our approach, to management of patients who experience these reactions, but in general, we would now not rechallenge patients as there are other alternative agents.[(30)]

The choice of non platinum second or subse-

Table 1. Response Rates to Second Line Therapy According to Treatment Free Interval (TFI) or Platinum Free Interval (PFI)

TFI (months)	Patients	Response
0-3	50	10%
7-12	17	29%
13-18	8	63%
19->21	17	94%

Blackledge et al 1989[11]

TFI (months)	Patients	Response
<12	35	26%
13-24	15	33%
>24	22	77%

Gore et al 1990[12]

P.F.I (months)	Response
>24	60%
12-24	33%
6-12	27%

Markman et al 1991[13]

PFI - Progression free-interval

Table 2. Responses to Second Line Therapy
(compilation of many studies and includes platinum sensitive and platinum resistant disease)

Agent	Response %
Paclitaxel[14,15,16]	22
Topotecan[17,18,19]	17
Liposomal doxorubicin[20,21]	18
Etoposide[22,23,24]	22
Gemcitabine[25,26]	18
Docetaxel[28]	23
Vinorelbine[29]	29
Tamoxifen[9,10]	11

Table 3. Response to Second Line Therapy According to Potential Platinum Sensitivity or Resistance

	Response Rate (%)	
Agent	Platinum. Sensitive	Resistant
Topotecan[17,18,19]	28	13
Paclitaxel[14,15,16]	25	12
Etoposide[22,23,24]	28	21
Gemcitabine[25,26]	29	13
Docetaxel[28]	-	23

quent line chemotherapy is based on many factors including likelihood of benefit, potential toxicity, schedule and convenience to the patient, as well as organ function and residual toxicity from prior treatment.[27] The options include oral etoposide, paclitaxel either weekly or every 3 weeks, docetaxel either weekly or every 3 weeks, topotecan daily for 5 days every 3 weeks, liposomal doxorubicin, or gemcitabine. All have activity in women with recurrent ovarian cancer but have different toxicities. The response rates are generally similar and the results of studies are influenced by the patient population treated.

In order to be eligible for entry to phase 2 trials, patients must have measurable disease, but such patients are not necessarily representative of those seen in the clinic who have an elevated CA125 titre but no measurable disease.

The question of the equivalence between pegylated liposomal doxorubicin monotherapy, paclitaxel or topotecan has been addressed in 2 separate phase 3 trials. Of 474 patients with ovarian cancer who relapsed after platinum based therapy, no significant differences were detected between the groups with respect to objective response rates or progression free survival.[21] However, the subgroup with platinum sensitive disease had a significant improvement in median progression free survival with pegylated liposomal doxorubicin vs topotecan (28.9 weeks vs 23.3 weeks, $p = 0.03$). A significant difference in overall survival was also noted in this group with a median survival of 108 weeks in the platinum sensitive group treated with liposomal doxorubicin compared to 71 weeks in the group treated with topotecan.

A separate study comparing paclitaxel 175mg/m^2 every 3 weeks with 50mg/m^2 liposomal doxorubicin every 4 weeks found them to be equivalent with respect to overall response rate (24% vs 17%) and progression free survival (21.7 vs 22.4 weeks) and overall survival (45.7 vs 56.1 weeks).[31]

A large phase 3 study of topotecan vs paclitaxel 175mg/m^2 every 3 weeks found that patients with platinum resistant ovarian cancer had a 13.3% response with topotecan and 6.6% with paclitaxel, while the response rates in patients with potentially platinum sensitive disease were 28.8% with topotecan and 20% with paclitaxel.[32] There was an apparent benefit in favor of topotecan noted initially with respect to time to progression but this was not significant with longer follow up.[33] These data suggest that liposomal doxorubicin is probably the agent of choice in the second line setting given the relative convenience of administration,toxicity profile and efficacy, but we would always use carboplatin initially in patients with platinum sensitive ovarian cancer.

To date, there have been no published randomized trials that have demonstrated a benefit of combination therapy over single agents in the second line setting. However this question is being addressed in a number of studies including the large ICON 4 trial, which has recruited 800 patients. Patients are randomized to receive either platinum alone (carboplatin/cisplatin) or a combination of platinum and paclitaxel every 3 weeks. It has been our practice to use sequential single agents in the relapse setting, with the exception of those patients who relapse late, where consideration is given to platinum based combinations.

A relatively small group of patients receive more than 1 or 2 agents in the relapse setting, and there are only scanty data published on the benefits of treatment in this setting. They are usually patients with platinum sensitive disease who can be retreated with carboplatin on multiple occasions and still respond to treatment. They typically have prolonged treatment free intervals and durable responses. Anecdotally, we have observed that repeated responses to platinum appear to be more common in women with a family history of breast/ovarian cancer, a personal history of breast and ovarian cancers, and in those women known to have germ-line mutations in BRCA1 and particularly BRCA2, and we are in the process of analysing our experience. There is growing evidence to suggest that women with BRCA1 and BRCA2 related ovarian cancers have a better prognosis, possibly related to improved response to platinum, related to impaired DNA repair, and this fits with our clinical observations.[34]

It is essential to communicate clearly with patients when deciding on treatment after multiple drugs have failed, as the likelihood of benefit is low, particularly in patients with poor performance status and large volume disease, and we would advise cessation of chemotherapy and focusing more on symptomatic management. It is also very uncommon in our experience for chemotherapy to be of benefit in women who have clinical evidence of bowel obstruc-

tion, and if surgery is not indicated, medical management and palliative care should be instituted.

Most studies of chemotherapy for recurrent ovarian cancer have focussed on response rates and progression free survival and have not evaluated quality of life. Communication regarding the objectives of therapy is important, as up to 40% of women believed that cure was a realistic possibility in one recently published study.[35] The toxicities of the drugs used can impact on quality of life, and the potential benefits as well as potential side effects need to be carefully considered when making treatment decisions. In women with indolent tumors observation alone is a reasonable option .

Role of Surgery in Recurrent Ovarian Cancer

The role of secondary cytoreductive surgery for patients with recurrent epithelial ovarian cancer has not been clearly defined, because many of the studies have included a heterogenous group of patients, making interpretation of results difficult.[36,40]

We recently reviewed our experience with secondary cytoreductive surgery at the Royal Hospital for Women for patients who developed recurrent disease after a disease free interval.[42] Patients were carefully selected pre-operatively, and those with ascites or widely disseminated disease were excluded. In this context, we were able to resect all macroscopic disease in 41% of 46 patients, with 35% of patients requiring intestinal resection.

Janicke et al report complete resection in 47% of 30 patients with 63% requiring intestinal resection.[37] The prospective study of Eisenkop et al employed aggressive techniques with the aim of removing all macroscopic disease.[36] En bloc resection techniques were used, including pelvic exenteration and ablative procedures using an argon beam coagulator or cavitron ultrasonic aspirator to eliminate peritoneal or serosal implants. They were able to achieve complete resection in 83% of their 36 patients.

Morbidity following surgery of this magnitude is of concern, and some series report a 2-3% mortality.[36,42] Prolonged paralytic ileus is common, and consideration should be given to parenteral hyperalimentation in these patients, particularly if they are undernourished pre-operatively, or require a large bowel resection. If anastomotic leak occurs, sepsis and enterocutaneous fistulae may result.

Our study demonstrated that aggressive secondary cytoreductive surgery can significantly prolong survival in two groups of patients: those in whom all macroscopic disease can be removed (Fig. 1), and those with a disease-free interval of 24 months or more (Fig. 2). The importance of disease-

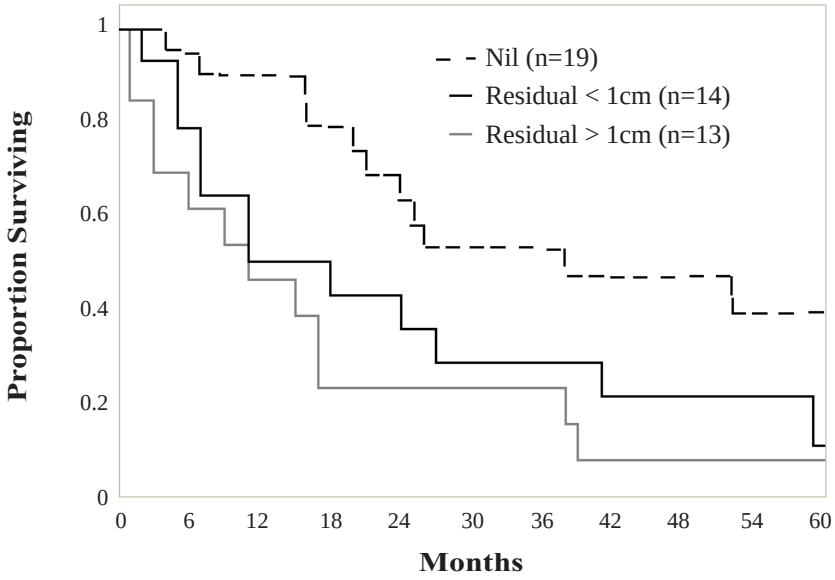

Fig. 1 Survival by residual disease after secondary cytoreduction. Reproduced from Tay et al.[42]

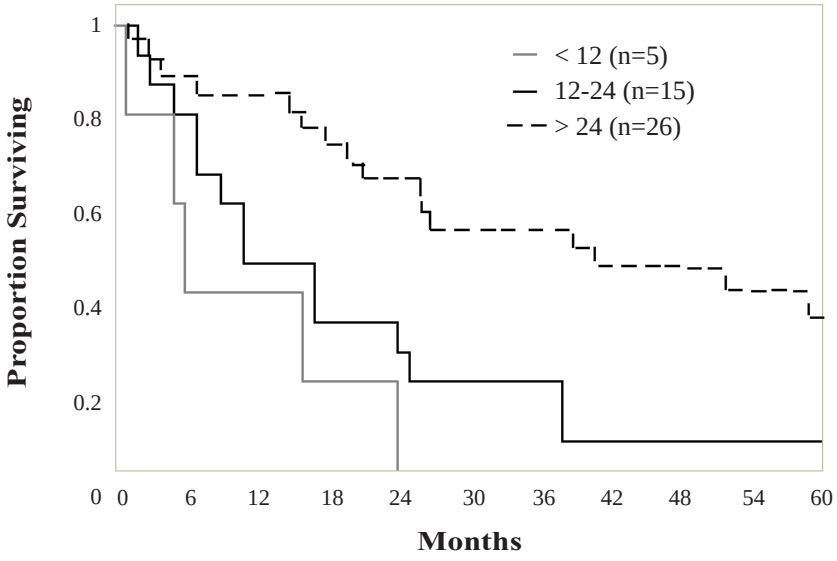

Fig. 2 Survival by disease-free interval after secondary cytoreduction. Reproduced from Tay et al.[42]

free interval has also been demonstrated in other studies, confirming that the longer patients survive, the more likely it is that they will be helped by early diagnosis of recurrent disease and appropriate management. Hence the need for long-term monitoring of all patients with CA-125 titres.

Role of Radiotherapy

In our series of 46 patients undergoing secondary cytoreductive surgery, there were 10 patients who received local radiation to the tumour bed following resection of localized disease.[42] Whole abdominal radiation has been more widely employed for patients with ovarian cancer, but it is too morbid in patients who have had multiple laparotomies, and as these patients have recurrent disease, it should be reasonable to treat the site of known disease. Several of our patients remained tumour-marker free for long intervals after this approach.

Conclusions

It is not possible to be prescriptive regarding the optimal approach to management of women with recurrent ovarian cancer, but we believe a multidisciplinary approach is ideal and should include palliative care and psycho-social support services in addition to the more traditional medical options.

REFERENCES

1. Hoskins P, Tu D, James K, et al. Factors predictive of survival after first relapse or progression in advanced epithelial ovarian carcinoma: a prediction tree analysis-derived model with test and validation groups. Gynecol Oncol 1998;70:224-30.
2 Eisenhauer EA, Vermorken JB, van Glabbeke M. Predictors of response to subsequent chemotherapy in platinum pretreated ovarian cancer: a multivariate analysis of 704 patients. Ann Oncol 1997;8:963-8.
3. Buller RE, Skilling JS, Sood AK, Plaxe S, Baergen RN, Lager DJ. Field cancerization: why late "recurrent" ovarian cancer is not recurrent. Am J Obstet Gynecol 1998; 178:641-9.
4. Guppy AE, Rustin GJS. CA125 Response: Can it replace the Traditional Response Criteria in Ovarian Cancer? The Oncologist, 2002;7:437-43.
5. Rustin GJ, Nelstrop AE, Tuxen MK, et al. Defining progression of ovarian carcinoma during follow-up according to CA 125: a North Thames Ovary Group Study. Ann Oncol 1996;7:361-4.
6. van der Burg ME, Lammes FB, Verweij J. The role of CA 125 in the early diagnosis of progressive disease in ovarian cancer. Ann Oncol 1990;1:301-2.
7. Vergote I, Rustin GJS, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors

(ovarian cancer). J Natl Cancer Inst 2000;92:1534-5.
8. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New Guidelines to evaluate the response to treatment in solid tumors. J. Natl Cancer Inst 2000;92:205-16.
9. Van Der Velden J, Gitsch G, Wain GV, Friedlander ML, Hacker NF. Tamoxifen in patients with advanced epithelial ovarian cancer Int J Gynecol Cancer 1995;5(4):301-5.
10. Williams CJ Tamoxifen for relapse of ovarian cancer. Cochrane Database Syst Rev 2000;(2):CD001034.
11. Blackledge G, Lawton F, Redman C, et al. Response of patients in phase II studies of chemotherapy in ovarian cancer: implications for patient treatment and the design of phase II trials. Br J Cancer 1989;59:650.
12. Gore ME, Fryatt I, Wiltshaw E, et al. Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds. Gynecol Oncol 1990;36:207-11.
13. Markman M, Rothman R, Hakes T, et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. J Clin Oncol 1991;9:389-93.
14. Thigpen JT, Blessing JA, Ball H, et al. Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: a Gynecologic Oncology Group study. J Clin Oncol 1994;12:1748-53.
15. Trimble EL, Adams JD, Vena D, et al. Paclitaxel for platinum-refractory ovarian cancer: results from the first 1,000 patients registered to National Cancer Institute Treatment Referral Center 9103. J Clin Oncol 1993;11: 2405-10.
16. Kohn EC, Sarosy G, Bicher A, et al. Dose-intense Taxol: high response rate in patients with platinum-resistant recurrent ovarian cancer. J Natl Cancer Inst 1994;86:18-24.
17. Kudelka AP, Tresukosol D, Edwards CL, et al. Phase II study of intravenous topotecan as a 5-day infusion for refractory epithelial ovarian carcinoma. J Clin Oncol 1996;14:1552-7.
18. Creemers GJ, Bolis G, Gore M, et al. Topotecan, an active drug in the second-line treatment of epithelial ovarian cancer: results of a large European phase II study. J Clin Oncol 1996;14:3056-61.
19. Bookman MA, Malmstrom H, Bolis G, et al.: Topotecan for the treatment of advanced epithelial ovarian cancer: an open-label phase II study in patients treated after prior chemotherapy that contained cisplatin or carboplatin and paclitaxel. J Clin Oncol 1998;16:3345-52.
20. Muggia FM, Hainsworth JD, Jeffers S, et al.: Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation. J Clin Oncol 1997;15:987-93.
21. Gordon AN, Fleagle JT, Guthrie D, et al. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 2001;19:3312-22.
22. Hoskins PJ, Swenerton KD. Oral etoposide is active against platinum-resistant epithelial ovarian cancer. J Clin Oncol 1994;12:60-3.
23. Rose PG, Blessing JA, Mayer AR, et al. Prolonged oral etoposide as second-line therapy for platinum-resistant and platinum-sensitive ovarian carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 1998;16:405-10.
24. Seymour MT, Mansi JL, Gallagher CJ, et al. Protracted oral etoposide in epithelial ovarian cancer: a phase II study in patients with relapsed or platinum-resistant disease. Br J Cancer. 1994;69:191-5.
25. Friedlander M, Millward MJ, Bell D, et al. A phase II study of gemcitabine in platinum pre-treated patients with advanced epithelial ovarian cancer. Ann Oncol 1998;9: 1343-5.
26. Lund B, Hansen OP, Theilade K, et al. Phase II study of gemcitabine (2',2'-difluorodeoxycytidine) in previously treated ovarian cancer patients. J Natl Cancer Inst 1994;86:1530-3.
27. Armstrong DK. Relapsed ovarian cancer: challenges and management strategies for a chronic disease. Oncologist 2002;7 Suppl 5:20-8.
28. Burger RA, DiSaia PJ, Roberts JA, et al. Phase II trial of vinorelbine in recurrent and progressive epithelial ovarian cancer. Gynecol Oncol 1999;72:148-53.
29. Rose PG, Blessing JA, Ball HG, Hoffman J, Warshal D, DeGeest K, Moore DH. A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2003;88:130-5.
30. Jones R, Ryan M, Friedlander M. Carboplatin hypersensitivity reactions: re-treatment with cisplatin desensitisation. Gynecol Oncol 2003;89:112-5.
31. O'Byrne KJ, Bliss P, Graham JD, et al. A phase III study of Doxil/Caelyx versus paclitaxel in platinum-treated, taxane-naive relapsed ovarian cancer. Proc Am Soc Clin Oncol. 2002;21:203a. [Abstract 808.]
32. Ten Bokkel Huinink W, Gore M, Carmichael J, et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. J Clin Oncol 1997;15:2183-93.
33. Gore M, ten Bokkel Huinink W, Carmichael J, et al. Clinical evidence for topotecan-paclitaxel non-cross-resistance in ovarian cancer. J Clin Oncol 2001;19:1893-900.
34. Ben David Y, Chetrit A, Hirsh-Yechezkel G, et al. National Israeli Study of Ovarian Cancer. Effect of BRCA mutations on the length of survival in epithelial ovarian tumors. J Clin Oncol 2002;15(20):463-6.
35. Doyle C, Crump M, Pintilie M, Oza AM. Does palliative chemotherapy palliate? Evaluation of expectations, outcomes, and costs in women receiving chemotherapy for advanced ovarian cancer. J Clin Oncol 2001;19:1266-74.
36. Eisenkop SM, Friedman RL, Wang HJ. Secondary cytoreductive surgery for recurrent ovarian cancer. Cancer 1995; 76:1606-14.
37. Janicke F, Holscher M, Kuhn W, von Hugo R, Pache L,

Siewert JR, et al. Radical surgical procedure improves survival time in patients with ovarian cancer. Cancer 1992;70:2129-36.
38. Vaccarello L, Rubin SC, Vlamis V, Wong G, Jones WB, Lewis JL, et al. Cytoreductive surgery in ovarian carcinoma patients with a documented previously complete surgical response. Gynecol Oncol 1995;57:61-5.
39. Morris M, Gershenson DM, Wharton T, Copeland LJ, Edwards CL, Stringer CA. Secondary cytoreductive surgery for epithelial ovarian cancer. Gynecol Oncol 1989;34:334-8.
40. Berek JS, Hacker NF, Lagasse LD, Nieberg RK, Elashoff RM. Survival of patients following secondary cytoreductive surgery in ovarian cancer. Obstet Gynecol 1983;61: 189-93.
41. Segna RA, Dottino PR, Mabdeli JP, Konsker K, Cohen CJ. Secondary cytoreduction for ovarian cancer following cisplatin therapy. J Clin Oncol 1993;11:434-9.
42. Tay EH, Grant PT, Gebski V, Hacker NF. Secondary cytoreductive surgery for recurrent epithelial ovarian cancer. Obstet Gynecol 2002;99:1008-13.