available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Management of partially platinum-sensitive relapsed ovarian cancer

*Stanley B. Kaye**

The Gynecologic Unit and the Drug Development Unit, Royal Marsden Hospital, Sutton Surrey, United Kingdom

ARTICLE INFO

Article history:
Received 15 October 2007
Received in revised form
7 December 2007
Accepted 7 December 2007

Keywords:
Ovarian neoplasms
Anthracyclines
Doxorubicin
Carboplatin
Taxoids
Antineoplastic agents

ABSTRACT

A platinum-taxane doublet has been established as the standard of care in the initial chemotherapy for ovarian cancer. Treatment at relapse is based largely on the platinum-free interval (PFI). Women with a PFI of 6–12 months are said to be partially platinum-sensitive. Based on the evidence from randomised trials, many clinicians offer treatment to this group with a platinum-containing doublet (including paclitaxel or gemcitabine). A promising third option under investigation is the combination of liposomal doxorubicin (PLD) with carboplatin. However, monotherapy with drugs such as PLD or carboplatin is an accepted alternative, and treatment is often chosen on an individual basis or because of the availability of an appropriate clinical study. Extending the PFI by the use of non-platinum monotherapy such as PLD at first-relapse may theoretically be helpful, but would need confirmation in prospective randomised trials.

1. Introduction

The most commonly used initial chemotherapy regimen for ovarian cancer is a platinum-taxane regimen.[1] It is estimated that approximately 80% of women with ovarian cancer will relapse and require second-line therapy.[2] The choice of second-line treatment is typically based on the duration of response to the initial platinum-based regimen (i.e. platinum-free interval or PFI). Response to second-line therapy and prognosis are also linked to PFI, with both improving as the PFI increases. Patients with an initial PFI less than 6 months are described as platinum-resistant. If the disease actually progresses during treatment (as opposed to relapsing after treatment discontinuation) it is described as platinum-refractory. Patients with a PFI greater than 6 months are deemed platinum-sensitive. Within this group, patients with a PFI of 6–12 months are often considered partially platinum-sensitive. While it is established that a carboplatin-containing doublet provides a survival advantage compared with carboplatin monotherapy in patients with platinum-sensitive relapsed ovarian cancer (ROC),[3,4] the extent of that benefit in the subgroup of partially platinum-sensitive is debatable, and the management of this subgroup continues to present challenges.

Because most patients are treated with a platinum-containing regimen at the time of initial diagnosis, the PFI and RFI (relapse-free interval) at the time of initial relapse are generally the same. This does not apply when considering further relapses, when the PFI and the RFI may be quite different. The clinical relevance is that in relapsed disease, patients deemed to have platinum-resistant disease at one point may still benefit from platinum at a later time point.

1.1. *Agents demonstrating efficacy in partially platinum-sensitive ROC*

1.1.1. *Carboplatin*

Carboplatin is well tolerated and the response in women with ovarian cancer relapsing 6–12 months after completion of ini-

* Tel.: +44 20 86613539; fax: +44 20 86613541.
E-mail address: stan.kaye@rmh.nhs.uk

1359-6349/$ - see front matter
doi:10.1016/j.ejcsup.2007.12.003

tial treatment with a platinum compound is approximately 30%.[4] Because the response rate increases to as high as 60% or more in women with a PFI of 12 months or more after completion of previous platinum-based chemotherapy,[3,4] it may be beneficial to defer the use of carboplatin in the 6–12 month setting. There are non-randomised retrospective data to support the contention, at least that some patients with platinum-resistant disease can regain platinum sensitivity after intervening treatment with another agent.[5,6] However, no randomised trials of this approach have been reported.

1.1.2. *Non-carboplatin options*

While carboplatin may be the most frequently used agent in women with platinum-sensitive ROC (PFI > 6 months), numerous non-platinum agents have demonstrated comparable activity (Table 1) when used as monotherapy in partially platinum-sensitive patients. Each agent is associated with a unique safety profile. Typically, serious adverse events can be effectively managed; however, there are toxicities that, while not life-threatening, can be particularly bothersome (e.g. alopecia). These toxicities should be taken into consideration when selecting the best treatment for a particular patient.

Randomised phase III data are available for four non-platinum agents in platinum-sensitive ROC: paclitaxel, pegylated liposomal doxorubicin (PLD), topotecan and gemcitabine.[9–14] The trials reporting on paclitaxel versus topotecan[9,10] and PLD versus topotecan[11,12] are published in full (Table 2). Trials reporting on PLD versus paclitaxel [13] and PLD versus gemcitabine[14] are published in abstract form only and data are limited.

Paclitaxel was compared with topotecan in 226 women with ROC; approximately 50% had platinum-sensitive disease (RFI > 6 months). The objective response rate was higher in platinum-sensitive patients receiving topotecan, but the difference was not statistically significant. At long-term follow-up, paclitaxel was associated with a pronounced survival benefit (significance not reported) in the platinum-sensitive group. Myelosuppression was the most common adverse event in both treatment groups, with Grade 4 myelosuppression reported in 79% of patients receiving topotecan and 23% receiving paclitaxel as second-line therapy and 81% and 23%, respectively, receiving third-line therapy. Grade 4 thrombocytopenia was also more common in topotecan-treated patients.[9,10] No results were reported for the subgroup of patients with partially platinum-sensitive ROC.

Topotecan was compared with PLD in 474 women with recurrent ovarian cancer. Patients were classified as platinum-sensitive ($n = 220$) if they had a PFI > 6 months after first-line platinum chemotherapy. The response rates were nearly identical in both treatment groups, but there was a superior progression-free survival as well as a statistically significant survival benefit in platinum-sensitive patients treated with PLD (108 versus 70 weeks, $p = .017$). The survival benefit was maintained when overall survival was analysed in the subgroup of partially platinum-sensitive patients with a PFI of 6–12 months (Fig. 1). No data are available on treatment given to patients on either arm once the disease had progressed following either PLD or topotecan. It is conceivable that the difference in overall survival could be partly explained if subsequent treatment patterns differed, e.g. more patients on the PLD arm receiving subsequent carboplatin.

While a similar percentage of women in each treatment group experienced Grades 1, 2 and 3 adverse events, more topotecan-treated women experienced Grade 4 events (71.1% versus 17.2%). The most common adverse events in patients receiving PLD were hand–foot syndrome (HFS) (49%) and stomatitis (40%). Most HFS was Grades 1–3. Grade 4 HFS

Table 1 – Non-platinum agents in ROC[7,8]

Agent	Response rate, % (relapse-free interval >6 months)	Toxicity leading to quality of life issues
Docetaxel	24–36	Hypersensitivity, diarrhoea, fluid retention
Etoposide	34	Alopecia, GI toxicity
Gemcitabine	34	Flu-like constitutional symptoms, hepatic dysfunction, dyspnea
Paclitaxel	20–45	Alopecia, peripheral neuropathy, arthralgias/myalgias
Pegylated liposomal doxorubicin	28	Hand–foot syndrome, mucositis
Topotecan	33	Asthenia, alopecia, schedule of administration
Vinorelbine	29	Constipation, nausea, peripheral neuropathy

Table 2 – Fully published randomised trials of non-platinum single-agent therapy of platinum-sensitive relapsed ovarian cancer

Author, year	Treatment (*n*)	Objective response	Overall survival	Comments
ten Bokkel Huinink (1997, 2004)[5,6]	Paclitaxel (55)	20.0%	85.1 weeks	Grade 4 neutropenia:
	Topotecan (52)	28.8% (*P* = .213)	63.4 weeks (*P* – NR)	Paclitaxel = 23% Topotecan = 79–81%
Gordon (2001, 2004)[7,8]	PLD (109)	28.4%	107.9 weeks	Grade 4 adverse events:
	Topotecan (111)	28.8% (*P* = .964)	70.1 weeks (*P* = .017)	PLD = 17.2% Topotecan = 71.1%

NR, not reported.

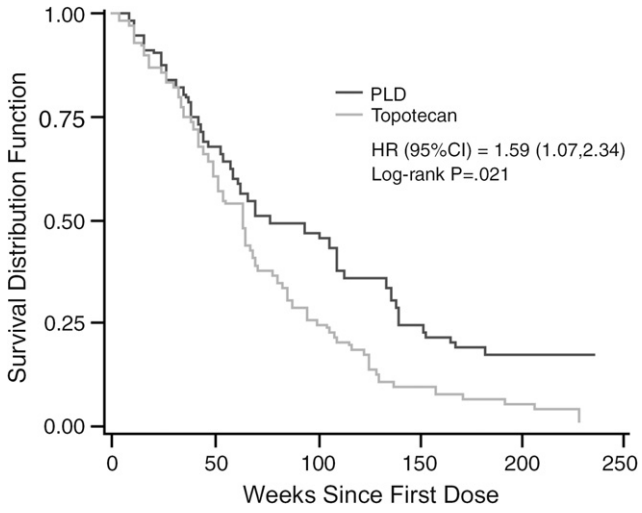

Fig. 1 – Pegylated liposomal doxorubicin (PLD) versus topotecan. Survival in patients relapsing 6–12 months after completing first-line platinum-based therapy. (With permission from Colombo and Gore, 2007[4].)

occurred in <1% of patients. Haematologic adverse events were common with topotecan, with 81% of patients experiencing neutropenia, 72% anaemia, 65% thrombocytopenia and 63% leukopenia. Alopecia was also more common with topotecan compared with PLD (49% versus 16%).[11,15]

PLD and paclitaxel were compared in 214 taxane naïve women with ROC that recurred after or did not respond to first-line treatment with a platinum-based regimen. The proportion of platinum-sensitive patients was not reported. There were no statistically significant between-group differences in objective response rate, progression-free survival (PFS), or overall survival. When patients were stratified by first-line platinum response, there were no significant differences in PFS or overall survival for platinum sensitive patients. While the number of adverse events was similar in each arm, patients treated with PLD experienced more nausea, vomiting, stomatitis and HFS and patients treated with paclitaxel experienced more alopecia, myalgia, arthralgia and paresthesia.[13]

The most recent phase III data are for PLD versus gemcitabine. Patients had ROC, failed only one line of a platinum-paclitaxel doublet, and had a PFI of 12 months or less. Approximately, 50% of patients (78 of 147) had a PFI of 6–12 months. PLD and gemcitabine exhibited similar activity in the overall population. Data were not presented separately for the partially platinum-sensitive population. More patients in the gemcitabine group had Grades 3 and 4 leukopenia (9% versus 22%; $p = .03$). There were no statistically significant differences in non-haematologic toxicities.[14]

1.2. *Platinum versus non-platinum agent at first relapse*

The choice of carboplatin-based or non-carboplatin-based treatment for partially platinum-sensitive patients is not straightforward and may best be made on an individual basis. In addition, the tendency to use a non-carboplatin-based treatment may be higher if the PFI is 6–8 months, whereas a carboplatin-based treatment may be favoured if the PFI is 10–12 months. Whenever possible, entry into a prospective randomised trial is the preferred option. The potential benefit of artificially prolonging the PFI by the use of a non-platinum-containing regimen at first relapse has been investigated at MD Anderson Cancer Center[5,6] and by the SOCRATES investigators.[16]

In two series of patients with a RFI < 6 months, treatment was initiated with non-platinum agents before retreatment with platinum. The median PFI when platinum was eventually given was 15 months and clinical benefit ranged from 39% in the earlier series (1995) to 68% in the most recent series (1996–2002). All responders had a PFI of at least 12 months[5,6] The conclusion to be drawn from these data is that the use of repeat single-agent carboplatin in platinum-resistant patients may be justified after treatment with a non-platinum-containing regimen.

In Italy, the SOCRATES investigators conducted a retrospective study to determine the impact of extending the PFI with a non-platinum agent in women with a relapse-free interval (RFI) of at least 6 months.[16] Patients from 37 centres were treated between 2000 and 2002. Data were available for 428 patients, of whom 40% had a RFI of 6–12 months. A total of 282 patients received a platinum agent at first relapse after a median RFI of 19 months and achieved a response rate of 74% (group A). Sixty-seven partially platinum-sensitive patients (median RFI 9.6 months) achieved a response rate of 45% after treatment with a non-platinum agent. Upon relapse (median PFI 23 months), these partially platinum-sensitive patients received a platinum agent and achieved a response rate of 57% (group B). A second group of 79 partially platinum-sensitive patients (median RFI 8.4 months) received platinum at first relapse and achieved a response rate of only 29% (group C). The difference in response to second-line platinum versus delayed platinum was statistically significant ($p = .02$). Median overall survival was similar in patients who were platinum-sensitive with a RFI > 12 months and patients who were partially platinum-sensitive (RFI 6–12 months) and received delayed platinum treatment (27.3 versus 26.1 months). Median overall survival was more than 35% lower in partially platinum-sensitive patients who received a platinum as second-line therapy (16.8 months).[16]

A prospective randomised trial is warranted to confirm these findings suggesting that extending the platinum-free interval may be beneficial in patient with partially platinum-sensitive ROC.

1.3. *Monotherapy versus combination therapy with carboplatin*

Several platinum-containing doublets have been compared with monotherapy. The ICON4 AGO OVAR 2.2 phase III trial compared paclitaxel plus a platinum-based regimen (paclitaxel plus carboplatin in 80%) with conventional platinum-based chemotherapy (carboplatin monotherapy in 71%) in 802 women with ROC and a PFI of at least 6 months. The platinum-taxane regimen was associated with an improved response rate (66% versus 54%, $p = .06$), improved PFS (12 months versus 9 months; HR = 0.76, $p = .0004$), and improved overall survival (29 months versus 24 months; HR = 0.82, $p = .02$). The impact of combination therapy versus conven-

tional platinum therapy on overall survival was somewhat less in patients with a PFI of 6–12 months compared with >12 months, but the difference was not statistically significant (Fig. 2). The doublet was associated with higher rates of alopecia and more Grades 2–4 neurological toxicity. Patients in the carboplatin alone group experienced more moderate to severe haematologic toxicities.[3]

The AGO OVAR 2.5 phase III trial randomised 356 patients with platinum-sensitive disease (PFI ⩾ 6 months) to carboplatin alone or carboplatin plus gemcitabine. Progression-free survival was significantly longer in patients receiving carboplatin plus gemcitabine (8.6 months versus 5.8 months; HR 0.72; 95% confidence interval (CI) 0.58–0.90, $p = .0031$).[17] Improved PFS was maintained in patients whose PFI was 6–12 months (7.9 months versus 5.2 months; HR 0.69, 95% CI 0.49–0.97; $p = .0311$) (Fig. 3). In the overall population, response rate favoured the doublet (47.2% versus 30.9%, $p = .0016$). Overall survival was similar in the two groups (18.0 versus 17.3 months) but the study was not powered for an overall survival end-point. Grades 3 and 4 haematologic toxicity (anaemia, neutropenia, thrombocytopenia) was significantly more common in patients receiving the doublet ($p < .001$). The incidence of Grade 3 or 4 non-haematologic toxicities was similar in both groups; however, Grade 2 alopecia was reported in 14.3% of patients receiving the combination and 2.3% receiving carboplatin alone.[17]

A phase II study evaluating the combination of PLD plus carboplatin offers additional insight. Of 105 women with ROC and a PFI of 6 months or more enrolled in the study, 43 had a PFI of 6–12 months. All patients received prior treatment with platinum and a taxane and were receiving second- or third-line therapy. The objective response rate was 63%. Median PFS was 9.4 months in the overall population, 11.4 months in patients with a treatment-free interval (TFI) > 12 months, and 7.9 months in patients with a TFI of 6–12 months ($p = .001$ for TFI > 12 months versus 6–12 months). A similar pattern was observed for overall survival, with median survivals of 32 months, 36 months and 21 months, respectively ($p = .006$ for TFI > 12 months versus 6–12 months). These responses and survival data compare favourably with those reported in ICON-4 and the AGO OVAR 2.5 trial, albeit in different studies. In this phase II trial, the proportions of (less favourable) patients with a PFI of 6–12 months and more extensive prior therapy were actually higher than in the two randomised trials (Table 3). Most non-haematologic toxicity was Grades 1 or 2. There was limited alopecia (33% Grades 1 and 2) and neurotoxicity (27% Grades 1 and 2, 1% Grade 3) and no Grade 3 or 4 HFS. Grade 3 or 4 haematologic toxicities included neutropenia (51%), leukopenia (27%), thrombocytopenia (26%), anaemia (12%) and febrile neutropenia (3%).[18]

In view of these promising data a phase III study has been initiated to compare the efficacy of a PLD plus carboplatin regimen with that of paclitaxel plus carboplatin (CALYPSO) in patients with platinum-sensitive ROC (PFI > 6 months). The trial will shortly complete its accrual target of 800 patients, with the first analysis expected in late 2008.

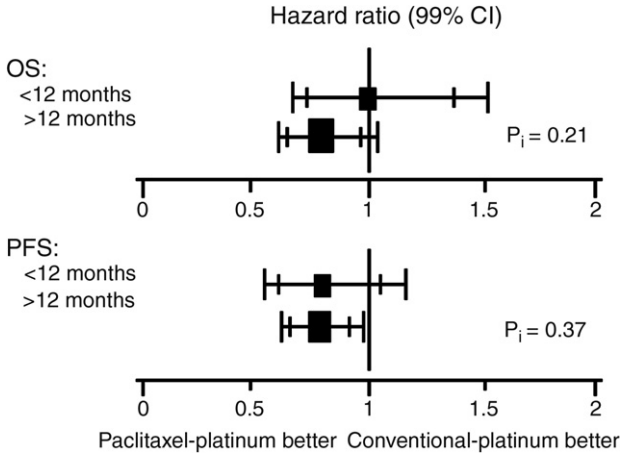

Fig. 2 – Overall survival (OS) and progression-free survival (PFS) in patients treated with a paclitaxel-platinum doublet (primarily paclitaxel plus carboplatin) versus a conventional platinum regimen (primarily carboplatin alone) in the ICON4 AGO OVAR 2.2 trial.[3]

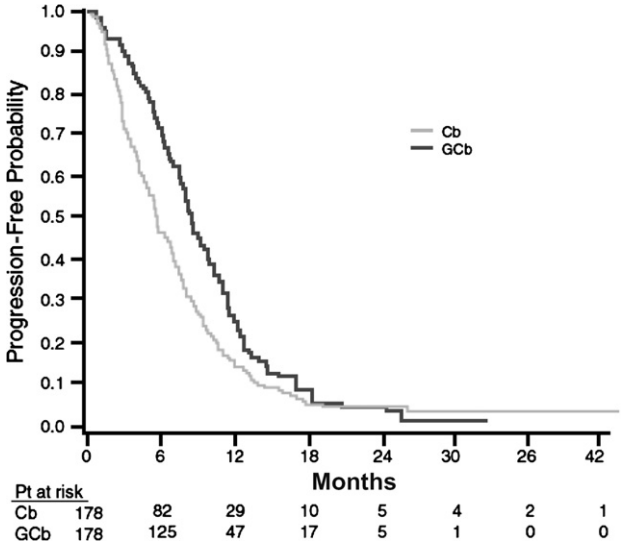

Fig. 3 – Progression-free survival (PFS) in patients with a platinum-free interval of 6–12 months treated with carboplatin alone (Cb) or carboplatin plus gemcitabine (GCb).[17]

2. Discussion and conclusions

At present there are two trials which have been most influential in formulating policy for treating partially platinum-sensitive ROC. These are the ICON-4 and the AGO-OVAR gemcitabine trials. In many centres, such patients are now treated with either paclitaxel–carboplatin or gemcitabine–carboplatin. A third option, that of PLD–carboplatin, is also given regularly, although as yet there are no substantial randomised data demonstrating equivalence or superiority to paclitaxel–carboplatin. One randomised trial has been reported, comparing PLD–carboplatin with carboplatin in platinum-sensitive recurrent ovarian cancer. Although an analysis did suggest superiority for PLD–carboplatin, the small number of patients recruited (total of 61) preclude any firm conclusions.[19] The results of the CALYPSO trial will therefore be particularly important, since it is quite conceivable that the toxicity profile of

Table 3 – Combination regimens evaluated for second-line therapy in platinum-sensitive patients

Study	PLD + carboplatin	Paclitaxel + carboplatin	Gemcitabine + carboplatin
	Ferrero et al. (2007)[16]	ICON4 AGO OVAR 2.2 Trial[3]	AGO OVAR 2.5, NCIC and EORTC GCG Trial[15]
Patient characteristics			
Number of patients	105	392	178
% TFI 6–12 months	43%	23%	40%
% TFI >12 months	53%	77%	60%
Prior therapies			
% with 1	60%	90%	100%
% with ⩾2	40%	10%	0
% prior taxanes	100%	43%	70%
Efficacy results in total population/patients with 6–12 month TFI			
OR (CR)	63% (38%)/NR	66% (NR)/NR	47% (15%)/NR
PFS, median	9.4 months/7.9 months	12 months/NR	8.6 months/7.9 months
OS	32 months/21 months	29 months/NR	18 months/NR

CR, complete response; NR, not reported; OR, objective response; OS, overall survival; PFS, progression-free survival; TFI, treatment-free interval.

PLD–carboplatin will prove superior to paclitaxel–carboplatin or gemcitabine–carboplatin given in this context. In partially platinum-sensitive patients with a PFI approaching 6 month (i.e. PFI 6–9 months), it may be helpful to prolong the PFI by the administration of monotherapy with an agent such as PLD. This strategy may allow for a higher response rate to subsequent platinum treatment. A phase III study is required to confirm the benefit of prolonging the PFI by administering a non-platinum agent at first relapse.

Another possible approach to consider is the introduction of non-platinum-containing combination regimes. While various doublets have been assessed, none have been subject to randomised comparison against a single (non-platinum) agent. The first such trial involves a new cytotoxic agent – Yondelis[20] and the trial (which includes partially platinum-sensitive patients with ROC) compares single agent PLD with a Yondelis-PLD combination. It has recently completed accrual and first results are expected in the near future.

The goal of ROC treatment is no longer just palliation, but prolonging survival. This is achieved by administering a new line of chemotherapy at each relapse. An additional approach may be the administration of maintenance regimens. The selected maintenance regimen should be well tolerated during long-term therapy. One small trial and a report of three cases have been published in which PLD was well tolerated when administered for up to 6 years in women with ROC.[21,22] A maintenance strategy opens up the potential for considering alternative forms of treatment other than chemotherapy. Targeted agents, particularly those aimed at inhibiting angiogenesis through VEGFR inhibition, are particularly attractive in this context, and a number of trials of this approach are now underway.

Other novel approaches to the management of partially platinum-sensitive ROC include resistance modulation based on the concept that drug resistance (to carboplatin) results from gene hypermethylation and silencing of damage recognition genes (e.g. *hMLH1*).[23] Data to support this notion have been provided within the framework of the SCOTROC-1 trial, which involved first-line treatment of ovarian cancer patients.

When plasma DNA of patients with ovarian cancer was examined before treatment with carboplatin-taxane chemotherapy and again at relapse, the number of patients with *hMLH1* methylation was found to increase. DNA in the plasma is known to have been shed by tumour; hence, it is a reliable and important marker for tumour behaviour. Acquisition of *hMLH1* methylation was predictive of poor overall survival.[23] In vitro data suggest that methylation of *hMLH1* may be associated with increased resistance to cisplatin and carboplatin and that restoration of *hMLH1* expression using the demethylating agent, decitabine, increases sensitivity.[24] Thus, identification of acquired *hMLH1* methylation may prove to be helpful in selecting patients who may derive particular benefit from demethylation therapies, such as decitabine, to restore platinum sensitivity. In the UK, Cancer Research UK is conducting a clinical trial in which patients with partially platinum-sensitive ROC are randomised to treatment with carboplatin alone or carboplatin plus decitabine. An earlier phase I trial has confirmed the feasibility of the decitabine–carboplatin combination, and also showed that demethylation did indeed occur in tumour samples at well tolerated doses.[25]

In the next few years, a range of randomised clinical trials will report data which may help in decision making for the treatment of patients with partially platinum-sensitive ROC. One which is not yet agreed or underway is the trial which would answer the question of prolongation of the PFI in order to increase platinum efficacy. Hopefully this gap will be addressed by one of the excellent cooperative groups devoted to the treatment of this disease.

Conflict of interest statement

S.B.K. is a member of Advisory Boards for Johnston & Johnston and Schering Plough and has received honoraria from both companies.

REFERENCES

1. Piccart MJ, Bertelsen K, James K, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results [see comments]. *J Natl Cancer Inst* 2000;**92**(9):699–708.
2. Pérez-López ME, Curiel T, Gómez JG, Jorge M. Role of pegylated liposomal doxorubicin (Caelyx) in the treatment of relapsing ovarian cancer. *Anticancer Drugs* 2006;**18**:611–7.
3. The ICON and AGO Collaborators. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer; the ICON4/AGO-OVAR-2.2 trial. *Lancet* 2003;**361**:2099–106.
4. Colombo N, Gore M. Treatment of recurrent ovarian cancer relapsing 6–12 months post platinum-based chemotherapy. Crit Rev Oncol/Hematol doi:10.1016/j.critrevonc.2007.04.004.
5. See HT, Freedman RS, Kudelka AP, et al. Retrospective review: re-treatment of patients with ovarian cancer with carboplatin after platinum resistance. *Int J Gynecol Cancer* 2005;**15**:209–16.
6. Kavanagh J, Tresukosol D, Edwards C, et al. Carboplatin reintroduction after taxane in patients with platinum-refractory epithelial ovarian cancer. *J Clin Oncol* 1995;**13**:1584–8.
7. Armstrong DK. Relapsed ovarian cancer: challenges and management strategies for a chronic disease. *Oncologist* 2002;**7**(Suppl. 5):20–8.
8. Herzog TJ. Recurrent ovarian cancer: how important is it to treat to disease progression? *Clin Cancer Res* 2004;**10**:7439–49.
9. 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.
10. ten Bokkel Huinink W, Lane SR, Ross GAon behalf of the International Topotecan Study Group. Long-term survival in a phase III, randomised study of topotecan versus paclitaxel in advanced epithelial ovarian carcinoma. *Ann Oncol* 2004;**15**:100–3.
11. Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol* 2001;**19**:3312–22.
12. Gordon AN, Tonda M, Sun S, Rackoff Won behalf of the Doxil Study 30-49 investigators. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. *Gynecol Oncol* 2004;**95**:1–8.
13. 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 (abstract 808). *Proc Am Soc Clin Oncol* 2002;**21**:203a.
14. Ferrandine G, Lorusso D, Pignata S, et al. A randomized phase III study of gemcitabine (GEM) versus pegylated liposomal doxirubicin (PLD) in progressive/recurrent ovarian cancer (OC), 2007 ASCO meeting proceedings part I. *J Clin Oncol* 2007;**18S**:LBA5506.
15. Gordon AN, Teitelbaum A. Overall survival advantage for pegylated liposomal doxorubicin compared to topotecan in recurrent epithelial ovarian cancer (abstract and poster). *Eur J Cancer Suppl* 2003;**1**:S51.
16. Pignata S, Odicino F, Scambia G, et al. Extending the platinum-free interval (PFI) with a non-platinum therapy in platinum (P)-sensitive recurrent ovarian cancer (OC): results from the SOCRATES retrospective study, 2006 ASCO annual meeting proceedings part I. *J Clin Oncol* 2006;**15**(18S):5093.
17. Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an Intergroup trial of the AGO-OVAR, and the NCIC CTG, and the EORTC GCG. *J Clin Oncol* 2006;**24**:4699–707.
18. Ferrero J-M, Weber B, Geay J-F, et al. Second-line chemotherapy with pegylated liposomal doxorubicin and carboplatin is highly effective in patients with advanced ovarian cancer in late relapse: a GINECO phase II trial. *Ann Oncol* 2007;**18**:263–8.
19. Alberts DS, Liu PY, Wilczynski S, et al. Phase III randomized trial of pegylated liposomal doxorubicin (PLD) plus carboplatin versus carboplatin in platinum-sensitive (PS) patients with recurrent epithelial ovarian or peritoneal carcinoma after failure of initial platinum-based chemotherapy: Southwest Oncology Group Protocol S0200, 2007 ASCO meeting proceedings part I. *J Clin Oncol* 2007;**25**(18S):5551.
20. Sessa C, DeBrand F, Perotti A, et al. Trabectedin for women with ovarian carcinoma after treatment with platinum and taxanes fails. *J Clin Oncol* 2005;**23**:1867–74.
21. Andreopoulou E, Gaiotti D, Kim E, et al. Pegylated liposomal doxorubicin HCL (PLD; Caelyx/Doxil): experience with long-term maintenance in responding patients with recurrent epithelial ovarian cancer. *Ann Oncol* 2007;**18**:716–21.
22. Collins Y, Lele S. Long-term pegylated liposomal doxorubicin use in recurrent ovarian carcinoma. *J Natl Med Assoc* 2005;**97**:1414–6.
23. Gifford G, Paul J, Vasey PA, Kaye SB, Brown R. Group obotSGCT. The acquisition of hMLH1 methylation in plasma DNA after chemotherapy predicts poor survival for ovarian cancer patients. *Clin Cancer Res* 2004;**10**:4420–6.
24. Plumb JA, Strathdee G, Sludden J, Kaye SB, Brown R. Reversal of drug resistance in human tumor xenografts by 2′-deoxy-5-azacytidine-induced demethylation of the hMLH1 gene promoter. *Cancer Res* 2000;**60**:6039–44.
25. Lee C, Appleton K, Plumb J, et al. A Phase I trial of decitabine in combination with carboplatin, both given 4 weekly by i.v. injection in patients with advanced solid tumours. *Proc Am Soc Clin Oncol* 2004;**23**:128.