PERGAMON

European Journal of Cancer 38 (2002) 1701–1707

European Journal of Cancer

www.ejconline.com

Review

Ovarian cancer: progress and continuing controversies in management

Charlotte Moss, Stan B. Kaye*

Department of Medical Oncology, Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, UK

Received 14 May 2002; accepted 16 May 2002

Abstract

Ovarian cancer is the most lethal of the gynaecological cancers, affecting approximately 1 in 75 women in the developed world. In most cases (>75%), the disease is disseminated beyond the ovary at diagnosis. For patients with stage III–IV disease, many clinicians agree that standard treatment should comprise six cycles of paclitaxel–carboplatin. Randomised trials over the past 10 years have indicated the superiority of paclitaxel-based treatment and that carboplatin is equivalent to cisplatin, but better tolerated. A recent trial has suggested that docetaxel may be a better option than paclitaxel, with reduced neurotoxicity and comparable efficacy. Overall treatment results remain unsatisfactory, since the median survival for these patients is 2–3 years. Future progress may be made by addressing the following issues: Would sequential regimes be more effective? Intriguing results from two large randomised trials (ICON-3 and GOG-132) indicate that single agent platinum might well be incorporated into such regimes. Additionally, a range of other agents could be tested as part of first-line regimes, having demonstrated activity in relapsed patients; these include topotecan, gemcitabine and liposomal doxorubicin. Newer agents, such as cell signalling inhibitors have shown potential as single agents, but may be particularly effective in combination with current drugs. Real progress can be expected when a better understanding is achieved of the mechanisms underlying clinical drug resistance in ovarian cancer, and a close laboratory–clinical interaction is crucial.

Keywords: Ovarian cancer; Management; Sequential regimes; New agents

1. Introduction

Ovarian cancer affects approximately 1 in 75 women in the developed world and is the most lethal of the gynaecological cancers. Over 75% of cases present at an advanced stage, with disease spread beyond the ovaries. Despite high rates of response to initial chemotherapy (up to 80%), the majority of women relapse, eventually with drug-resistant disease. There is an overall 5-year survival of 30%. This article (based on the teaching lecture given by Professor S.B. Kaye at ECCO II in Lisbon in October 2001), is intended to outline current practice, as well as recent advances, controversies and future prospects for treatment.

2. Principles of management

2.1. Surgery

The treatment modalities of surgery and chemotherapy are interdependent: Adequate surgical staging is necessary to select patients who will benefit from adjuvant chemotherapy.

Optimal de-bulking of the tumour mass to <2 cm improves the response rate to chemotherapy and improves length of progression-free survival, and overall survival. In patients where initial optimal de-bulking is not possible, a survival advantage (6 months), has been demonstrated for interval de-bulking surgery in addition to chemotherapy [1].

These results have prompted investigation into the approach of primary treatment with chemotherapy rather than surgery. A recent study comparing neo-adjuvant

* Corresponding author. Tel.: +44-20-8642-6011.
E-mail address: skaye@icr.ac.uk (S.B. Kaye).

0959-8049/02/$ - see front matter
PII: S0959-8049(02)00161-2

chemotherapy (three cycles platinum agent and paclitaxel) followed by tumour de-bulking and three further cycles of chemotherapy versus conventional treatment (de-bulking and six cycles of chemotherapy) in 64 patients with advanced disease (stage IIIc with >500 ml ascites) demonstrated a higher tumour resection rate and a significant survival advantage (42 versus 23 months) [2]. Results of further trials are awaited to assess this interesting approach more thoroughly.

The value of specialist gynaecology oncology surgeons is difficult to quantify in the absence of randomised trials. However, careful retrospective studies have suggested a survival benefit in the order of 25% at 3 years compared with initial management by general surgeons [3].

2.2. First-line chemotherapy

In general, chemotherapy is offered to patients with stage Ic disease or above, (disease confined to one or both ovaries with positive peritoneal washings or ascites). The most effective treatment in epithelial ovarian carcinoma is platinum-based chemotherapy, first introduced in the form of cisplatin in the mid-1970s.

An improvement in efficacy was demonstrated in the mid-1990s with the addition of paclitaxel to the platinum regimes. Gynaecological Oncology Group trial 111 (GOG) 111 provided the first report of a survival benefit (12 months) using paclitaxel (over 24 h) and cisplatin compared with cyclophosphamide–cisplatin in sub-optimally de-bulked patients [4]. This benefit was confirmed in the Intergroup trial OV-010 in patients both with minimal and bulky residual disease using cisplatin and paclitaxel given over 3 h [5]. Subsequently, the equivalence of carboplatin–paclitaxel to cisplatin–paclitaxel has been confirmed, at least in terms of follow-up survival data so far, in three trials (including >1500 patients) with both minimal and bulky residual disease, with carboplatin being the better tolerated [6–8].

Consequently, de-bulking surgery followed by paclitaxel–carboplatin has become the 'gold standard' first-line treatment. The usual regime is of 6×3-weekly cycles of carboplatin area under the concentration curve (AUC) 5–7.5 given over 1 h plus paclitaxel 175 mg/m^2 given over 3 h.

2.3. Improving first-line treatment

Despite the advances in first-line chemotherapy, the median survival for epithelial ovarian carcinoma is only 2–4 years. Current trials, aimed at optimising first-line treatment are examining a variety of issues including: the choice of taxane, the incorporation of newer drugs, sequential treatment, duration of treatment, and role of intraperitoneal (i.p.) therapy.

2.3.1. Choice of taxane

Recent clinical data suggest that docetaxel, a semi-synthetic taxane with a superior preclinical profile, is at least equally effective to paclitaxel with significant differences in its side-effect profile. Docetaxel has shown a response rate of 28% in platinum-refractory patients and activity in paclitaxel-refractory patients (23% response rate) [9].

As a first-line treatment, a recent dose-finding study in 140 patients found 3-weekly carboplatin AUC 5 and docetaxel 75 mg/m^2 to be the optimal schedule with over 90% of patients receiving the full six courses, only 6% having grade 2–3 neurotoxicity and a median progression-free survival of 17 months. This compares favourably with rates of 30% sensory neuropathy using carboplatin–paclitaxel regimes [10].

A multicentre, randomised trial comparing docetaxel–carboplatin versus paclitaxel–carboplatin in a total of 1077 patients showed equivalence in the response rates and progression-free survival, but significant differences in toxicity. Paclitaxel caused significantly more neurotoxicity (30% >grade 1 neurotoxicity versus 11% with docetaxel), leading to early treatment discontinuation. Docetaxel showed a higher incidence of neutropenia compared with paclitaxel. However, this was not associated with an increase in treatment discontinuation or toxic deaths [11]. This experience has been replicated in a phase II study in the USA, although Markman and colleagues did note a high rate (34%) of hypersensitivity using docetaxel in combination with carboplatin [12].

2.3.2. Incorporation of new drugs into first-line treatment

A number of different drugs have shown activity in recurrent ovarian cancer, including:

Anthracyclines:	epirubicin, liposomal doxorubicin
Topoisomerase inhibitors:	etoposide, topotecan
Antimetabolites:	gemcitabine
Vinca alkaloids:	vinorelbine
Platinum analogues:	oxaliplatin

The observation of activity in platinum pretreated patients has prompted the investigation of some of these as first-line agents. The options for incorporation of newer drugs into first-line treatment include: concurrent triplet regime, new doublet with carboplatin, sequential treatment with new doublets, sequential single agents (Table 1).

A phase I/II study conducted by the Arbeitgemeinschaft Gynakologische Onkologie (AGO) group in Germany demonstrated the safety of the triplet regime of epirubicin 60–75 mg/m^2, paclitaxel 175 mg/m^2 and carboplatin AUC 7 [13]. A subsequent randomised trial comparing this with carboplatin–paclitaxel was recently completed. Preliminary results for the whole

Table 1
Completed and ongoing studies

Group	Regime	Where X is:
AGO, EORTC	paclitaxel–carboplatin/X (versus paclitaxel–carbo)	Epirubicin
AGO	paclitaxel–carboplatin→X	Topotecan
GOG	X/carboplatin→paclitaxel–carboplatin	Topotecan, lipsomal doxorubicin, gemcitabine
NCIC, EORTC	cisplatin/X→paclitaxel–carboplatin	Topotecan
Scottish Group	carboplatin→docetaxel–X	Gemcitabine, CPT11

carbo, carboplatin; AGO, EORTC, European Organisation for Research and Treatment of Cancer; NCIC, National Cancer Institute of Canada.

group show the addition of epirubicin caused increased myelotoxicity with no significant differences in progression-free survival or overall survival [14].

Hansen and colleagues [15] showed that therapy with gemcitabine, paclitaxel and carboplatin seems both a feasible and very active combination, albeit with substantially more myelotoxicity than two drug regimens. Two successive studies in chemotherapy-naïve patients showed overall response rates approaching 100% (with complete responses in 60%) and a median survival of >30 months so far. Randomised trials including this combination have begun in Europe and North America.

2.3.3. Sequential treatment

There are a number of reasons why sequential treatment is worthy of exploration in the first-line treatment of ovarian cancer. Firstly, there is the concern that concurrent use of three or more cytotoxic agents may be prohibitively toxic. Sequential treatment may be more tolerable and give greater scope for the addition of new agents.

Secondly, the unexpected results from two randomised controlled trials (GOG 132 [16] and International Collaborative Ovarian Neoplasma (ICON) 3 [17]) showed no benefit for the addition of paclitaxel to cisplatin/carboplatin regimes. This, together with the observation that there is a myeloprotective effect (reduction in thrombocytopenia) when paclitaxel is added to platinum regimes, has led to the notion that there may be a degree of antagonism when these are given concurrently. Experimental data in this regard are equivocal.

Both trials conclude that formal randomised studies examining the option of sequential therapy are a logical next step. Sequential therapy allows initial therapy with full doses of the best single agent in ovarian cancer, i.e. carboplatin.

In vitro, ovarian cancer cells with mutant p53 are resistant to cisplatin but exhibit hypersensitivity to paclitaxel [18]. Using these agents sequentially may allow us to capitalise on these differences.

2.3.4. Maintenance therapy

The question of the optimal treatment duration, i.e. maintaining chemotherapy beyond apparent clinical complete remission has been considered for several years. Previous trials of maintenance treatment in ovarian cancer have been unsuccessful, mainly due to the cumulative side-effects of platinum-based therapy. Maintenance therapy with paclitaxel is currently under investigation following the observation that in addition to its effect on microtubule formation, it has anti-angiogenic properties. There are encouraging preliminary data from a randomised South Western Oncology Group (SWOG) trial in which paclitaxel was given for 12 months following induction therapy and further trials incorporating weekly paclitaxel are proposed.

Maintenance therapy is also being investigated with non-cytotoxic approaches such as immunotherapy: A recent phase I/II trial involved 42 patients with relapsed epithelial ovarian cancer previously treated with platinum-based chemotherapy. They were vaccinated with a murine monoclonal anti-idiotypic antibody against CA-125, (intended to mobilise a tumour-specific immune response). 64% of patients developed non-specific human anti-mouse antibodies, 66% developed specific anti-CA-125 antibodies. The median overall survival in patients with a positive immune response was 19.9 months versus 5.3 months in those with no demonstrable anti-CA-125 response [19]. Further follow-up on this trial is awaited with interest.

2.3.5. Intraperitoneal therapy

I.p. administration of chemotherapy offers opportunities for exposing tumour cells to high doses of drug with low systemic effects. Given that in the majority of cases of epithelial ovarian cancer the disease remains within the peritoneal cavity (60%), it seems a logical approach. However, physiological studies have shown that the penetration from the outer surface of a peritoneal tumour nodule remains a major hurdle, and it seems likely that any clinical benefit will be limited to patients with microscopic peritoneal metastases.

In a large US Intergroup study, an 8-month survival benefit was demonstrated in a trial with i.p. administration of cisplatin and intravenous (i.v.) cyclophosphamide

versus standard i.v. cisplatin–cyclophosphamide in patients with stage III ovarian cancer [20].

The i.p. administration of targeted radiation therapy, following conventional chemotherapy has been assessed through the i.p. administration of a beta particle emitter (Yttrium-90), bound to a monoclonal antibody to MUC 1. Non randomised trials suggested a survival benefit from this approach and the results of a large randomised trial are awaited [21].

3. Recurrent disease/second-line therapy

The aim of treatment in recurrent disease is palliative; therefore the priority must be to maintain quality of life. An important principle for many clinicians would be not to initiate chemotherapy simply on the basis of rising CA-125 levels in the absence of symptoms. Patients are divided into two groups, according to the length of time since first-line platinum-based therapy:

1. *Platinum-refractory*: Patients who have progressed on or within 6 months of platinum-based chemotherapy.
2. *Platinum-sensitive*: Patients with a progression-free interval of >6 months after the primary therapy.

This division reflects the expected response rate to subsequent chemotherapy. Platinum-refractory patients can expect a response rate of $<20\%$; this increases to approximately 30% for a 6–12 month treatment-free interval and $\geqslant 50\%$ when the interval exceeds 12 months [22,23]. Patients with platinum-sensitive disease may respond to re-challenge with the initial therapy. Current trials are exploring whether there is any benefit in these patients for the addition of other drugs to single agent platinum (generally carboplatin).

There is no standard second-line treatment for patients with either platinum- or paclitaxel-refractory disease. Some patients would be eligible for treatment in clinical trials of new agents or new approaches (e.g. the assessment of weekly cisplatin given with hypertonic saline). There are a number of cytotoxic agents with known activity in recurrent disease (Table 2).

3.1. Novel agents

New drugs for ovarian cancer fall into two categories: (a) cytotoxic agents, (b) non-cytotoxics. A sample of cytotoxic agents under evaluation is provided in Table 3. This includes examples of analogues of existing agents, developed to circumvent drug resistance, as well as new

Table 2
Agents used for recurrent disease

Agent	Regime	Ref.	No. of patients	O.R.R. (%)	Median survival	Toxicities/comments:
Etoposide Topoisomerase II inhibitor	50 mg/m^2 p.o. days 1–21/28	[24]	99 41 Pt-res. (25 Pt + Tax res.) 41 Pt-sensitive	 27 32 34	 10.8 months 16.5 months	25% G4 neutropenia
Topotecan Topoisomerase I inhibitor	1.5 mg/m^2 days 1–5/21	[25,26]	251 Pt-resistant Pt-sensitive	 $\sim$13 19–29	11–15 months	$\sim$80% G4 neutropenia 30% G4 thrombocytopenia
Liposomal doxorubicin (caelyx)	50 mg/m^2 day 1/28	[27]	219 192 Pt-res.	12.3 9–15	Median response duration 6 months	25% $\geqslant$ G3 stomatitis 25% $\geqslant$ G3 PPE $<$10% G4 neutropenia
Epirubicin (high dose)	150 mg/m^2 day 1/21	[28]	100 Pt-sensitive	20 41	Median response duration 9 months	
Gemcitabine Pyrimidine analogue	800–1250 mg/m^2 days 1, 8, 15/28	[29–32]	$>$100 Pt-resistant	 13–22	 6 months	 23% $\geqslant$ G3 neutropenia
Vinorelbine Vinca alkaloid	30 mg/m^2 days 1, 8/21	[33,34]	57 Pt-resistant	21	10.1 months	
Oxaliplatin	130 mg/m^2 day 1/21	[35]	45 32 Pt-resistant	16	10.5 months	Possible synergistic activity with other platinum agents
Tamoxifen Oestrogen receptor antagonist	20 mg od p.o.	[36]	623	9.6	Unable to assess	
PZA Pyrazoloacridine	750 mg/m^2 day 1/21	[37,38]	42 Pt-sensitive 24 Pt-resistant	24 8.5		

G, grade; pats, patients; Res, resistant; pt, platinum; p.o., orally; O.R.R., overall response rate; PPE, palmar-plantar erythrodysesthesia; od, once daily.

Table 3
Agents under investigation for activity in epithelial ovarian cancer

Agent	Dose	Ref.	
NX211 Liposomal lurtotecan	3.8 mg/m^2 day 1/21	[39]	DLT: neutropenia, thrombocytopenia
ZD 0473 Sterically hindered platinum	130 mg /m^2 day 1/21	[40]	Aims to overcome thiol-mediated platinum resistance. In phase II studies. DLT: myelosuppression
BR 3464 Triplatinum complex	0.12 mg/m^2 days 1–5/21	[41]	Pre-clinical studies show non-cross resistance with cisplatin DLT neutropenia, late onset diarrhoea
Capecitabine Fluoropyrimidine		[42]	Orally available. Established role in treatment of colorectal, breast and pancreatic Ca
Taxoprexin Taxane	1100 mg/m^2	[43]	Paclitaxel-fatty acid conjugate (docosahexaenoic acid (DHA)–paclitaxel). Prolongs half life, resulting in increased tumour AUC with reduced plasma AUC
BMS 184476 Taxane	60 mg/m^2 day 1/21	[44]	For phase II evaluation. DLT: neutropenia, diarrhoea, mucositis

AUC, area under the concentration curve; DLT, dose-limiting toxicity; Ca, cancers.

formulations of available drugs. An alternative approach is based on research into the mechanisms underlying tumorigenesis and progression and this has led to a plethora of new targets and potential agents for clinical use. Some of these may offer opportunities to modulate chemo-resistance, arguably the biggest obstacle to the advance of ovarian cancer treatment. New assays may allow the identification of specific molecular abnormalities in individual tumours and monitoring of the *in vivo* effect of a given agent. However, further evaluation in large randomised trials is needed to correlate the molecular abnormalities with clinical outcome.

One of the difficulties for the immediate future may be in determining where these agents 'fit in' in the context of current chemotherapy. For example, in patients with advanced disease conventional cytotoxic chemotherapy may be augmented by concurrent signal transduction inhibitors aimed at enhancing chemo-sensitivity, or, alternatively, it may be followed by single agent signal transduction inhibitors with the aim of maintaining a complete response through a different 'cytostatic' effect.

3.1.1. Signal transduction inhibitors (STIs)

Antitumour activity in patients with advanced ovarian cancer has been demonstrated in phase I studies with various STIs, including:

i. Bryostatin, a naturally occurring protein kinase C inhibitor (with agonist activity at certain doses). Single agent activity was noted in the first phase I trial in patients with advanced disease.
ii. Epidermal Growth Factor (EGF) receptor tyrosine kinase inhibitor (OSI 774), an oral antagonist demonstrated three partial responses in 34 heavily pretreated patients in a phase II trial, with a further 10 patients showing stable disease [45].
iii. Trastuzumab (Herceptin) is a humanised monoclonal antibody for the HER-2 receptor and licensed for use in breast cancer. Up to 20% of ovarian tumours also express this receptor [46].

3.1.2. Modulators of chemoresistance

PSC833 is a non-immunosuppressive analogue of Cyclosporin D which reverses P-glycoprotein mediated multidrug resistance. A recent phase II trial of PSC883 with paclitaxel included 60 patients with paclitaxel-resistant disease and showed a partial response rate of 8.6% [47]. A phase III trial with paclitaxel and carboplatin ± valspodar for first-line treatment has recently been completed.

Decitabine (5 aza-2-deoxycytidine) aims to target platinum resistance due to mismatch repair (MMR) deficiency. Low levels of expression of hMLH1 due to hypermethylation leads to a failure of cell death following cytotoxic induced DNA damage. Experimentally, hypomethylating agents such as decitabine can reverse platinum resistance in ovarian cancer cell lines. Clinical resistance can be examined by analysing tumour DNA (present in serum) for microsatellite instability. Earlier Scottish Group studies correlated loss of MMR at presentation with poor prognosis in ovarian cancer patients. Decitabine is currently in phase I trials in combination with carboplatin [48].

3.1.3. Anti-angiogenesis/anti-invasion agents

Vascular endothelial growth factor (VEGF) is secreted by ovarian cancer cells and appears to be an important factor in angiogenesis and the generation of ascites. Shrinkage of i.p. tumour in murine models has been achieved using an anti-VEGF receptor antibody. VEGF receptor(r) tyrosine kinase inhibitors are undergoing phase I trials and will eventually be evaluated in ovarian cancer.

Matrix Metalloprotease Inhibitors (MMPIs) are a new class of drug aimed at preventing tumour invasion. Randomised trials in ovarian and other cancers have so far proved negative, indicating that further consideration needs to be given to the appropriate clinical candidates to assess this approach.

3.1.4. Gene therapy

Ovarian carcinoma provides a good opportunity to investigate gene therapy techniques utilising the i.p. route to overcome problems with delivery of genetic agents. Loss of p53 function occurs in 50% of cases of advanced EOC and is associated with platinum resistance. Onyx 015, an attenuated adenovirus replicates only in cells with mutant p53. In a phase I trial of i.p. Onyx 015, 1 of 15 patients with ovarian cancer demonstrated virus replication in peritoneal washings [49]. Another approach has been to attempt to reintroduce wild-type p53 back into tumour cells to restore chemosensitivity. Using an adenoviral vector intraperitoneally, some evidence of TP53 transgene expression in ascitic fluid has been shown. A phase III trial using this approach in combination with platinum-based chemotherapy is now underway.

References

1. van der Burg ME, van Lent M, Buyse M, *et al*. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynaecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med* 1995, **332**, 629–634.
2. Kuhn W, Rutke S, Spathe K, *et al*. Neoadjuvant chemotherapy followed by tumor debulking prolongs survival for patients with poor prognosis in International Federation of Gynecology and Obstetrics Stage IIIC ovarian carcinoma. *Cancer* 2001, **92**, 2585–2591.
3. Junor EJ, Hole DJ, McNulty L, Mason M, Young J. Specialist gynaecologists and survival outcome in ovarian cancer: a Scottish national study of 1866 patients. *Br J Obstet Gynaecol* 1999, **106**, 1130–1136.
4. McGuire WP, Hoskins WJ, Brady MF, *et al*. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1964, **334**, 1–6.
5. 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. *J Natl Cancer Inst* 2000, **92**, 699–708.
6. Ozols RF. Paclitaxel (Taxol)/carboplatin combination chemotherapy in the treatment of advanced ovarian cancer. *Semin Oncol* 2000, **27**(Suppl. 7), 3–7.
7. du Bois A, Neijt JP, Thigpen JT. First line chemotherapy with carboplatin plus paclitaxel in advanced ovarian cancer—a new standard of care? *Ann Oncol* 1999, **10**(Suppl. 1), 35–41.
8. Neijt JP, Engelholm SA, Tuxen MK, *et al*. Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. *J Clin Oncol* 2000, **18**, 3084–3092.
9. Kaye SB. The integration of docetaxel into first-line chemotherapy for ovarian cancer. *Int J Gynecol Cancer* 2001, **11**(Suppl. 1), 31–33.
10. Vasey PA, Atkinson R, Coleman R, *et al*. Docetaxel-carboplatin as first line chemotherapy for epithelial ovarian cancer. *Br J Cancer* 2001, **84**, 170–178.
11. Vasey P, on behalf of the Scottish Cancer Trials Group. Preliminary results of the SCOTROC trial: a phase III comparison of paclitaxel-carboplatin and docetaxel-carboplatin as first line chemotherapy for stage Ic-IV ovarian cancer. *Proc ASCO* 2001, **20**, 202a.
12. Markman M, Kennedy A, Webster K, *et al*. Combination chemotherapy with carboplatin and docetaxel in the treatment of cancers of the ovary and fallopian tube and primary carcinoma of the peritoneum. *J Clin Oncol* 2001, **19**, 1901–1905.
13. du Bois A, Luck HJ, Bauknecht T, *et al*. First-line chemotherapy with epirubicin, paclitaxel, and carboplatin for advanced ovarian cancer: a phase I/II study of the Arbeitsgemeinschaft Gynakologische Onkologie Ovarian Cancer Study Group. *J Clin Oncol* 1999, **17**, 46–51.
14. Luck HJ, Du Bois A, Weber B, *et al*. The integration of anthracyclines in the treatment of advanced ovarian cancer. *Int J Gynecol Cancer* 2001, **11**(Suppl. 1), 34–38.
15. Hansen SW. Gemcitabine, platinum, and paclitaxel regimens in patients with advanced ovarian carcinoma. *Semin Oncol* 2002, **29**(Suppl. 1), 17–19.
16. Muggia FM, Braly PS, Brady MF, *et al*. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a gynecologic oncology group study. *J Clin Oncol* 2000, **18**, 106–115.
17. Colombo N. Randomised trial of paclitaxel (PTX) and carboplatin (CBDCA) versus a control arm of carboplatin or CAP (cyclophosphamide, doxorubicin & cisplatin: The Third International Collaborative Ovarian Neoplasm Study (ICON3). *Proc ASCO* 2000, **19**, 379a.
18. Cassinelli G, Supino R, Perego P, *et al*. A role for loss of p53 function in sensitivity of ovarian carcinoma cells to taxanes. *Int J Cancer* 2001, **92**, 738–747.
19. Wagner U, Kohler S, Reinartz S, *et al*. Immunological consolidation of ovarian carcinoma recurrences with monoclonal anti-idiotype antibody ACA125: immune responses and survival in palliative treatment. *Clin Cancer Res* 2001, **7**, 1154–1162.
20. Alberts DS, Liu PY, Hannigan EV, *et al*. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med* 1996, **335**, 1950–1955.
21. Nicholson S, Bell S, McCormack M, *et al*. A randomized phase III trial of adjuvant intraperitoneal radioimmuno-therapy in ovarian cancer. *Proc ASCO* 2000, **19**, 383a.
22. du Bois A. Treatment of advanced ovarian cancer. *Eur J Cancer* 2001, **37**(Supp. 9), S1–S7.
23. Harries M, Kaye SB. Recent advances in the treatment of epithelial ovarian cancer. *Expert Opin Investig Drugs* 2001, **10**, 1715–1724.
24. Rose PG, Blessing JA, Mayer AR, Homesley HD. 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**, 405–410.
25. 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**, 2183–2193.
26. 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**, 3345–3352.
27. Johnston SR, Gore ME. Caelyx: phase II studies in ovarian cancer. *Eur J Cancer* 2001, **37**(Suppl. 9), S8–S14.
28. Vermorken JB, Kobierska A, Chevallier B, *et al*. A phase II study of high-dose epirubicin in ovarian cancer patients previously

treated with cisplatin. EORTC Gynecological Cancer Cooperative Group. *Ann Oncol* 2000, **11**, 1035–1040.
29. 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**, 1343–1345.
30. Shapiro JD, Millward MJ, Rischin D, *et al*. Activity of gemcitabine in patients with advanced ovarian cancer: responses seen following platinum and paclitaxel. *Gynecol Oncol* 1996, **63**, 89–93.
31. Lund B, Hansen OP, Neijt JP, Theilade K, Hansen M. Phase II study of gemcitabine in previously platinum-treated ovarian cancer patients. *Anticancer Drugs* 1995, **6**(Suppl. 6), 61–62.
32. von Minckwitz G, Bauknecht T, Visseren-Grul CM, Neijt JP. Phase II study of gemcitabine in ovarian cancer. *Ann Oncol* 1999, **10**, 853–855.
33. Sorensen P, Hoyer M, Jakobsen A, *et al*. Phase II study of vinorelbine in the treatment of platinum-resistant ovarian carcinoma. *Gynecol Oncol* 2001, **81**, 58–62.
34. Bajetta E, Di Leo A, Biganzoli L, *et al*. Phase II study of vinorelbine in patients with pretreated advanced ovarian cancer: activity in platinum-resistant disease. *J Clin Oncol* 1996, **14**, 2546–2551.
35. Piccart MJ, Green JA, Lacave AJ, *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**, 1193–1202.
36. Williams CJ. Tamoxifen for relapse of ovarian cancer. *Cochrane Database Syst Rev* 2001, **1**, CD001034.
37. Plaxe SC, Blessing JA, Morgan MA, Carlson J. Phase II trial of pyrazoloacridine in recurrent platinum-resistant ovarian cancer: a Gynecologic Oncology Group study. *Am J Clin Oncol* 2002, **25**, 45–47.
38. Plaxe SC, Blessing JA, Bookman MA, *et al*. Phase II trial of pyrazoloacridine in recurrent platinum-sensitive ovarian cancer: a Gynecologic Oncology Group study. *Gynecol Oncol* 2002, **84**, 32–35.
39. Kehrer DF, Bos AM, Verweij J, *et al*. Phase I and pharmacologic study of liposomal lurtotecan, NX 211: urinary excretion predicts hematologic toxicity. *J Clin Oncol* 2002, **20**, 1222–1231.
40. Kelland LR, Sharp SY, O'Neill CF, *et al*. Mini-review: discovery and development of platinum complexes designed to circumvent cisplatin resistance. *J Inorg Biochem* 1999, **77**, 111–115.
41. Sessa C, Capri G, Gianni L, *et al*. Clinical and pharmacological phase I study with accelerated titration design of a daily times five schedule of BBR3464, a novel cationic triplatinum complex. *Ann Oncol* 2000, **11**, 977–983.
42. Vasey P, McMahon L, Paul J, Kaye SB. Phase II trial of capecitabine in relapsed ovarian cancer. *Ann Oncol* 2000, **11**(Suppl. 4), 84.
43. Bradley MO, Swindell CS, Anthony FH, *et al*. Tumor targeting by conjugation of DHA to paclitaxel. *J Control Release* 2001, **74**, 233–236.
44. Hidalgo M, Aylesworth C, Hammond LA, *et al*. Phase I and pharmacokinetic study of BMS-184476, a taxane with greater potency and solubility than paclitaxel. *J Clin Oncol* 2001, **19**, 2493–2503.
45. Finkler N, Gordon A, Crozier M, *et al*. Phase II evaluation of OSI-774, a potent oral antagonist of EGFR-TK in patients with advanced ovarian cancer. *Proc ASCO* 2001, **20**, 208a.
46. Hellstrom I, Goodman G, Pullman J, Yang Y, Hellstrom KE. Overexpression of HER-2 in ovarian carcinomas. *Cancer Res* 2001, **61**, 2420–2423.
47. Fracasso PM, Brady MF, Moore DH, *et al*. Phase II study of paclitaxel and valspodar (PSC 833) in refractory ovarian carcinoma: a gynecologic oncology group study. *J Clin Oncol* 2001, **19**, 2975–2982.
48. 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**, 6039–6044.
49. Vasey PA, Shulman LN, Campos S, *et al*. Phase I trial of intraperitoneal injection of the E1B-55-kd-gene-deleted adenovirus ONYX-015 (dl1520) given on days 1 through 5 every 3 weeks in patients with recurrent/refractory epithelial ovarian cancer. *J Clin Oncol* 2002, **20**, 1562–1569.