REVIEW

Platinum Resistance in Ovarian Cancer

Lesley D. Dunfield BScH[1] and Duane L. Guernsey PhD[2].
Departments of Pharmacology[1] and Pathology[2], Division of Molecular Pathology and Molecular Genetics. Dalhousie University, Halifax, Nova Scotia.

Chemotherapeutic drug resistance is a major impediment in the treatment of cancer. Platinum containing chemotherapeutic agents are the first-line therapy for the treatment of ovarian cancer. Unfortunately, resistance to platinum agents such as cisplatin and carboplatin commonly occurs in ovarian cancer patients. Numerous mechanisms such as enhanced DNA repair, decreased apoptosis, and increased drug export and elimination contribute to the occurrence of platinum resistance. Alternative therapies, combination chemotherapy, altered route of administration, and less conventional methods such as whole body hyperthermia have been developed in attempts to overcome platinum resistance and to enhance responsiveness in ovarian cancer patients. The commonly used method to overcome platinum resistance is administration of second line chemotherapeutic agents such as liposomal doxorubicin, taxanes, topotecan, and gemcitabine. Unfortunately, no unifying method exists to enhance responsiveness in platinum resistant ovarian cancer patients, and most patients resistant to platinum agents tend to be resistant to other chemotherapeutic agents as well. Mechanisms of platinum resistance and attempts to overcome this in ovarian cancer will be reviewed.

Corresponding Author: phone (902) 494 6348; fax (902) 494 1388; ldunfiel@is2.dal.ca

The objective of cancer treatment is to eliminate cancer cells, and this can be achieved by surgery, radiation therapy and chemotherapy[1]. Chemotherapy is the primary treatment for cancer, however, there are limitations. The successful treatment of many types of cancer has been severely hindered by the development of resistance to chemotherapeutic agents (drug resistance). Determining the mechanisms contributing to drug resistance is important in order to potentially bypass resistance and enhance patient responsiveness to chemotherapeutic agents. Drug resistance is thought to be multi-factorial and perhaps due to the co-existence of multiple mechanisms. Mechanisms believed to contribute to the occurence of platinum drug resistance in ovarian cancer will be reviewed.

Platinum containing chemotherapeutic agents such as cisplatin (Platinol®) and carboplatin (Paraplatin®) have proven effective in the treatment of numerous cancers[2,3]. These agents invoke cytotoxicity by inducing DNA damage through the formation of DNA-interstrand and intrastrand crosslinks[2-6]. When DNA damage is unable to be repaired, the damaged cells undergo programmed cell death (apoptosis).

Unfortunately, resistance to platinum containing drugs is common in cancer treatment[7]. Platinum containing chemotherapeutic agents are the first-line therapy used in the treatment of ovarian cancer[8]. However, greater than 50% of ovarian cancer patients acquire resistance to chemotherapeutic agents, including platinum agents, following initial treatment making further therapy ineffective[2,7,9]. Numerous mechanisms have been found that contribute to the occurrence of platinum resistance in ovarian cancer.

Cancer's Mechanisms of Resistance

Altered drug transport

Multi-drug resistance (MDR) is a phenomenon that occurs when cells are resistant to numerous drugs that are structurally unrelated[10]. Numerous drug resistant cancers have been shown to overexpress the drug transporters P-glycoprotein, multi-drug resistance related protein (MRP) and lung resistance related protein (LRP), which lead to increased efflux of drugs out of cancer cells[7,10,11]. Seventy-seven percent of ovarian cancers were found to overexpress LRP, which correlated with decreased sensitivity to treatment[7,8,12].

Glutathione

Glutathione (GSH) functions in membrane transport, drug inactivation and elimination by conjugation with substances such as platinum containing agents[1,11,13]. Therefore, overexpression of either GSH or the enzyme responsible for GSH conjugation, glutathione S-transferase (GST), results in decreased sensitivity to these agents[11,14]. The effect of GSH on platinum resistance has recently been investigated, and over-expression of GSH has been found in platinum resistant ovarian cancer cells. Studies by Mistry et al.[15] and Godwin et al.[16] correlated high levels of GSH to platinum resistance in ovarian cancer cell lines.

Accumulation and removal of adducts

The difference in accumulation versus removal of platinum-DNA adducts has been investigated in platinum sensitive and resistant cell lines. These studies concluded that the increased ability of cancer cells to remove DNA adducts formed by platinum compounds contributes to platinum resistance, and not decreased accumulation of adducts[17,18].

DNA repair

Enhanced DNA repair can lead to drug resistance by repairing the damage induced by DNA damaging chemotherapeutic agents[19-22]. Enhanced efficiency of DNA repair has been shown to be a common mechanism of platinum resistance[20,22,23]. Studies by Masuda et al.[20] and Lai et al.[22] demonstrated increased DNA repair in a cisplatin resistant ovarian cancer cell line compared to the cisplatin sensitive

parental cell line. The authors concluded that sensitive cells are unable to effectively recognize and repair the lesions caused by cisplatin treatment, thereby leading to cytotoxicity[22]. In addition, overexpression of DNA repair proteins has been implicated in platinum resistant ovarian cancer cells and patients. The repair proteins DNA polymerase b, ERCC1 and XPAC have been found to be overexpressed in platinum resistant ovarian cancer cells or patients[24-26].

Alternatively, cells deficient in DNA mismatch repair (MMR) are unable to recognize damaged DNA and induce apoptosis, also resulting in resistance[27-29]. MMR plays a role in recognition of DNA adducts formed by platinum agents causing apoptosis of the damaged cell. Therefore, cells with defective MMR will be unable to recognize these adducts and fail to induce apoptosis, thereby resulting in platinum resistance[27,28].

Modulation of apoptosis

To this end, failure to induce apoptosis is an additional mechanism for the occurrence of drug resistance, by allowing cancer cells to survive the damage induced by chemotherapeutic agents[19,21]. The tumor suppressor gene p53 is the most commonly mutated gene in cancer, and functions in regulation of the cell cycle and induction of apoptosis[1,30]. Modulation of p53 can therefore cause drug resistance by failure of the damaged cells to induce apoptosis following damage[11,31]. A recent study revealed that resistance to platinum therapy was significantly correlated with mutated or over-expressed p53[32]. Branch et al.[19] studied the role of p53 mutants and defective MMR and found mutated p53, not defective MMR, to be the major cause of cisplatin resistance in ovarian cancer cells. This study contradicts results reported above, however, a comparative analysis was not done between p53 status and MMR to investigate a potential role for p53[27-29]. Although MMR-induced apoptosis can also occur via a p53 independent pathway[33,34], studies by Wu et al.[34] indicated both MMR and p53 are likely necessary for apoptosis induced by chemical agents, such as cisplatin.

Clearly, studies to date have not agreed upon a single mechanism responsible for the occurrence of platinum resistance in ovarian cancer, and likely, it is a combination of mechanisms that may impede successful treatment. In an effort to bypass the hindrance of platinum resistance common to ovarian cancer treatment, additional treatment regimes are being studied with hopes of improving patient responsiveness.

Overcoming Platinum Resistance

Since numerous mechanisms are involved in platinum resistance, many approaches have been investigated to overcome platinum resistance. Some therapies focus on mechanisms to enhance sensitivity to platinum by increasing tumor cytotoxicity, cellular uptake, and biodistribution. Alternative therapies have been tested alone and in combination with platinum to enhance ovarian cancer patient responsiveness in platinum refractory disease.

Glutathione depletion

As discussed above, GSH overexpression can contribute to the occurrence of platinum resistance in ovarian cancer, therefore decreasing levels of GSH can potentially bypass this mechanism of resistance[11,14-16,35]. Buthionine sulfoximine (BSO) can decrease cellular levels of GSH in cancer patients, with approximately 50% of cancer patients showing markedly decreased cellular levels of GSH[36]. Although BSO alters sensitivity to platinum and other agents in cancer cells[35-37], this treatment was not directly correlated with increased sensitivity to platinum in ovarian cancer patients and is not used clinically. Future therapies, however, may utilize BSO to increase responsiveness to platinum therapy in ovarian cancer patients with elevated GSH levels.

Cyclosporin A

Cyclosporin A (Neoral®, Sandimmune®) has been implicated in the reversal of resistance to chemotherapeutic agents[38]. Cyclosporin A and platinum combination therapy resulted in only a minimal response rate in platinum resistant ovarian cancer, indicating that this treatment would not to be effective in platinum resistant ovarian cancer[39-41].

Liposomal encapsulation of chemotherapeutic agents

Encapsulation of drugs in liposomes is emerging as a useful drug delivery mechanism, due to low toxicity and the potential to alter pharmacokinetic properties[42]. Liposomal encapsulated cisplatin has been tested for activity and has been suggested to be useful to overcome platinum resistance[43,44]. The anti-tumor effect of one liposomal cisplatin agent, SPI-077, was superior compared to free cisplatin in terms of pharmacokinetics, biodistribution and cytotoxicity[44]. The possibility of increased drug exposure to tumor cells without increased side effects of liposomal cisplatin could be beneficial to platinum resistant ovarian cancer patients.

Other liposomal encapsulated chemotherapeutic agents such as doxorubicin (Caelyx®, Doxil®) are being used effectively in the treatment of platinum resistant ovarian cancer[45,46]. Liposomal doxorubicin could therefore be used as a possible alternative treatment for platinum resistant ovarian cancer patients to enhance responsiveness, and indeed is frequently used as second-line therapy in platinum resistant ovarian cancer patients.

Taxanes

Chemotherapeutic agents that differ in mechanism of action compared to platinum are being used for treatment of platinum resistant ovarian cancer. Taxanes, such as paclitaxel (Taxol®), have been found to be useful in the treatment of ovarian cancer[47]. Taxanes do not rely on p53 mediated induction of apoptosis for cytotoxicity[21]. A comparative study examining p53 status and sensitivity to either platinum or taxanes in ovarian cancer patients found mutant p53 conferred resistance to only platinum, whereas these patients remained sensitive to taxanes[21]. Hence, ovarian

cancer patients resistant to platinum therapy due to defective p53 remain sensitive to taxanes[21]. Paclitaxel is approved for first-line therapy and is used frequently for the treatment of advanced ovarian cancer patients resistant to platinum.

Combination therapy

Other research has addressed the possibility that platinum agents administered in combination with other chemotherapeutic agents could enhance responsiveness by acting via different mechanisms of action to increase cytotoxicity. Stiff et al.[48,49] investigated the co-administration of mitoxantrone (Novantrone®), carboplatin, and cyclophosphamide (Cytoxan®, Procytox®) followed by autologous bone marrow rescue in platinum resistant ovarian cancer patients compared to platinum sensitive patients. Forty-seven percent of resistant patients achieved complete response versus 88% of sensitive patients in a phase II study[49]. Although combination chemotherapy is commonly used, autologous bone marrow rescue is not used for the treatment of ovarian cancer, although it may be beneficial.

Platinum analogues

Oxaliplatin is a platinum analogue that has been shown to be cytotoxic to tumor cells resistant to cisplatin and carboplatin, including ovarian tumor cells. Oxaliplatin appears to be more effective at inducing DNA damage than cisplatin, due to utilization of a different mechanism of action[50]. MMR is necessary for cisplatin induced cytotoxicity, however, MMR does not play a role in oxaliplatin mediated cytotoxicity[50]. Hence, ovarian cancer patients resistant to cisplatin and carboplatin may be responsive to oxaliplatin, making oxaliplatin a potentially useful therapeutic option for platinum resistant ovarian cancer patients.

Whole body hyperthermia

Hyperthermia has been shown to enhance cytotoxicity and the therapeutic index of platinum[51-53]. Cellular accumulation of platinum and tumor cytotoxicity are increased by hyperthermia, whereas normal tissue toxicity is not greatly affected[51,52]. Estermann et al.[53] subjected platinum resistant ovarian cancer patients to whole body hyperthermia to raise systemic temperature to 41.8°C, followed by carboplatin treatment, and achieved a 35.7% response rate. The mechanism of action of this effect has not been determined, however, it is suggested that this change in temperature may cause drug accumulation and adduct formation to increase and DNA repair to decrease[53]. Although these results seem promising, hyperthermia is not a commonly used therapy to overcome resistance.

Aphidicolin

As described above, increased DNA repair can confer resistance to platinum agents[20,22]. Aphidicolin disrupts DNA repair via inhibition of DNA polymerases, hence, numerous studies have looked at the ability of aphidicolin treatment to overcome platinum resistance[22,54]. An in vivo study showed aphidicolin and platinum administered in combination can overcome platinum resistance[55]. A recent study determined that MMR deficient ovarian cancer cells resistant to platinum have increased platinum sensitivity following aphidicolin treatment[56]. Although the studies investigating aphidicolin indicate it could be useful, aphidicolin is not administered for the treatment of resistant ovarian cancer patients.

Intraperitoneal administration

Platinum agents are typically administered intravenously (I.V.), however, studies have shown that intraperitoneal (I.P.) administration of platinum agents can be more effective in the treatment of ovarian cancer[57-59]. Greater cisplatin levels were achieved in the peritoneal cavity resulting in greater survival and fewer side effects in a phase III study[57]. Thirty-six percent of the patients that received I.V. cisplatin responded to therapy, compared to 47% of patients treated intraperitoneally[57]. A critical limitation to this study is that patients were previously untreated; therefore, it is unknown whether the patients would have initially been sensitive to platinum therapy. A previous study by Kirmani et al.[59] treated ovarian cancer patients with persistent or recurrent disease who had previously failed treatment. This study demonstrated a complete response rate of 65%, indicating I.P. administered cisplatin therapy could circumvent platinum resistance[59]. I.P. administration may prove to be a mechanism to enhance responsiveness to platinum therapy in resistant tumors due to the enhanced exposure of the tumor cells to platinum[59].

Additional second-line therapies

In addition to the therapies discussed above, topotecan and gemcitabine are frequently used in platinum resistant ovarian cancer patients[60]. Topotecan (Hycamtin®) is a topoisomerase I inhibitor shown to be active in platinum resistant ovarian cancer and is indicated for second-line treatment[61,62]. The antimetabolite gemcitabine (Gemzar®) is frequently administered effectively in platinum resistant ovarian cancer patients[60,63].

Conclusion

Numerous mechanisms contribute to the occurence of platinum resistance in ovarian cancer, and consequently, numerous therapeutic strategies have been developed to overcome resistance. Furthermore, additional mechanisms to bypass platinum resistance not discussed in this review are being evaluated. Therapies to alter the specific resistance mechanism or enhance drug concentration without increasing the occurrence of adverse effects will prove useful to circumvent resistance to platinum agents. With the development of novel chemotherapeutic agents and more selective targeting strategies, ovarian cancer patient responsiveness can be enhanced resulting in improved patient survival and quality of life. The commonly used approach for the treatment of platinum resistant ovarian cancer is the co-administration of additional chemotherapeutic agents, such as topotecan, gemcitabine and liposomal

doxorubicin. Despite the advancement in this area, no unifying mechanism causes drug resistance, therefore, no single mechanism will be able to bypass resistance. Additional work is needed to further our understanding of the mechanisms surrounding platinum resistance and modalities to overcome this problem in ovarian cancer treatment.

References

1. King RJB. *Cancer Biology*. England: Pearson Education Ltd, 2000:89-95,233-252.
2. Perez RP. Cellular and molecular determinants of cisplatin resistance. *Eur J Cancer* 1998;34(10):1535-1542.
3. Roberts JJ, Thomson AJ. The mechanism of action of antitumor platinum compounds. *Prog Nucl Acid Res* 1979;22:71-133.
4. Zwelling LA, Kohn KW. Mechanism of action of cis-dicholordiammineplatinum(II) *Cancer Treatment Rep* 1979;63:1439-1444.
5. Douple EB. *Cis*-diamminedichloroplatinum(II): effects of a representative metal coordination complex on mammalian cells. *Pharmac Ther* 1984;25:297-326.
6. Eastman A. Characterization of the adducts produced in DNA by *cis*-diamminechloroplatinum(Ii) and *cis*-dichloro(ethylenediamine)platinum(II). *Biochemistry* 1983;22:3947-3933.
7. Giaconne G. Clinical perspectives on platinum resistance. *Drugs* 2000; 59(suppl.4);9-17.
8. Sood AK, Butler RE. Drug resistance in ovarian cancer: from the laboratory to the clinic. *Obstet & Gynecol* 1998;92:312-319.
9. Perez RP, Hamilton TC, Ozols RF. Resistance to alkylating agents and cisplatin: insights from ovarian carcinoma model systems. *Pharmac Ther* 1990;48:19-27.
10. Volm M. Multidrug resistance and its reversal. *Anticancer Res* 1998;18:2905-2918.
11. Harrison DJ. Molecular mechanisms of drug resistance in tumors. *J Pathol* 1995;175:7-12.
12. Izquierdo MA, van der Zee AG, Vermorken JB, van der Valk P, Belien JA, Giaconne G, Scheffer GL, Flens MJ, Pinedo HM, Kenemans P, etal. Drug resistance-associated marker Lrp for prediction of response to chemotherapy and prognoses in advanced ovarian carcinoma. *J Natl Cancer Inst* 1995;87:1230-1237.
13. Meister A, Anderson ME. Glutathione. *Ann Rev Biochem* 1983;52:711-760.
14. Helmbach H, Rossmann E, Kern MA, Schadendorf D. Drug-resistance in human melanoma. *Int J Cancer* 2001;93:617-622.
15. Godwin AK, Meister A, O'Dwyer PJ, Huang CS, Hamilton TC, Anderson ME. High resistance to cisplatin in human ovarian cancer cell lines is associated with marked increase of glutathione synthesis. *Proc Natl Acad Sci* 1992;89:3070-3074.
16. Mistry P, Kelland LR, Abel G, Sidhar S, Harrap KR. The relationships between glutathione, glutathione-S-transferase and cytotoxicity of platinum drugs and melphalan in eight human ovarian carcinoma cell lines. *Br J Cancer* 1991;64:215-220.
17. Masuda H, Tanaka T, Matsuda H, Kusaba I. Increased removal of DNA-bound platinum in a human ovarian cancer cell line resistant to cis-diamminedichloroplatinum(II). *Cancer Res* 1990;50:1863-1866.
18. Parker RJ, Eastman A, Bostick-Bruton F, Reed E. Acquired cisplatin resistance in human ovarian cancer cells is associated with enhanced repair of cisplatin-DNA lesions and reduced drug accumulation. *J Clin Invest* 1991;87:772-777.
19. Branch P, Masson M, Aquilina G, Bignami M Karran P. Spontaneous development of drug resistance: mismatch repair and p53 defects in resistance to cisplatin in human tumor cells. *Oncogene* 2000;19:3138-3145.
20. Lai G-M, Ozols RF, Smyth JF, Young RC, Hamilton TC. Enhanced DNA repair and resistance to cisplatin in human ovarian cancer. *Biochem Pharmacol* 1988;37:4597-4600.
21. Lavarino C, Pilotti S, Oggionni M, Gatti L, Perego P, Bresciani G, Pierotti MA, Scambia G, Ferrandina G, Fagotti A, Mangioni C, Lucchini V, Vecchione F, Bolis G, Scarfone G, Zunino F. p53 gene status and response to platinum/paclitaxel-based chemotherapy in advanced ovarian carcinoma. *J Clin Oncol* 2000;18(23):3936-3945.
22. Masuda H, Ozols RF, Lai G-M, Fojo A, Rothenberg M, Hamilton TC. Increased DNA repair as a mechanism of acquired resistance to cis-diamminedichloroplatinum(II) in human ovarian cancer cell lines. *Cancer Res* 1988;48:5713-5716.
23. Lindahl T, Wood RD. Quality control by DNA repair. *Science* 1999;286:1897-1905.
24. Cooper DN, Krawczak M, Antonarakis SE. The nature and mechanism of human gene mutation. In: Vogelstein B, Kinzler KW, ed. The genetic basis of human cancer. New York: McGraw-Hill, 1995:65-86.
25. Bergoglio V, Canitrot Y, Hogarth L, Minto L, Howell SB, Cazaux C, Hoffmann J-S. Enhanced expression and activity of DNA polymerase β in human ovarian tumor cells: impact on sensitivity towards antitumor agents. *Oncogene* 2001;20:6181-6187.
26. Dabholkar M, Vionnet J, Bostick-Bruton F, Yu JJ, Reed E. Messenger RNA levels of XPAC and ERCC1 in ovarian cancer tissue correlate with response to platinum-based chemotherapy. *J Clin Invest* 1994;94:703-708.
27. Aebi S, Kurdi-Haidar B, Gordon R, Cenni B, Zheng H, Fink D, Christen RD, Boland CR, Koi M, Fishel R, Howell SB. Loss of mismatch repair in acquired resistance to cisplatin. *Cancer Res* 1996;56:3087-3090.
28. Drummond JT, Anthoney A, Brown R, Modrich P. Cisplatin and Adriamycin resistance are associated with MutLα and mismatch repair deficiency in an ovarian tumor cell line. *J Biol Chem* 1996;271:19645-19648.
29. Samimi G, Fink D, Varki NM, Husain A, Hoskins WJ, Alberts DS, Howell SB. Analysis of MLH1 and MSH2 expression in ovarian cancer before and after platinum drug-based chemotherapy. *Clin Cancer Res* 2000;6:1415-1421.
30. Bálint É, Vousden KH. Activation and activities of the p53 tumor suppressor protein. *Br J Cancer* 2001;85:1813-1823.
31. Shah MA, Schwartz GK. Cell cycle-mediated drug resistance: an emerging concept in cancer therapy. *Clin Cancer Res* 2001;7:2168-2181.
32. Reles A, Wen WH, Schmider A, Gee C, Runnebaum IB, Kilian U, Jones LA, El-Naggar A, Minguillon C, Schönborn I, Reich O, Kreienberg R, Lichtenegger W, Press MF. Correlation of p53 mutations with resistance to platinum-based chemotherapy and shortened survival in ovarian cancer. *Clin Cancer Res* 2001;7:2984-2997.
33. Harfe BD, Jinks-Robertson S. DNA mismatch repair and genetic instability. *Annu Rev Genet* 2000;34:359-399.
34. Wu J, Gu L, Wang H, Geacintov NE, Lu G-M. Mismatch repair processing of carcinogen-DNA adducts triggers apoptosis. *Mol Cell Biol* 1999;19:8292-8301.
35. O'Dwyer PJ, Hamilton TC, Young RC, LaCreta FP, Carp N, Tew KD, Padavic K, Comis RL, Ozols RF. Depletion of glutathione in normal and malignant human cells in vivo by buthionine sulfoximine: clinical and biochemical results. *J Natl Cancer Inst* 1992;84:264-267.
36. O'Dwyer PJ, Hamilton TC, LaCreta FP, Gallo JM, Kilpatrick D, Halbherr T, Brennan J, Bookman MA, Hoffman J, Young RC, Comis RL, Ozols RF. Phase I trial of buthionine sulfoximine in combination with melphalan in patients with cancer. *J Clin Oncol* 1996;14:249-256.
37. Mistry P, Loh SY, Kelland LR, Harrap KR. Effect of buthionine sulfoximine on PtII and PtIV drug accumulation and the formation of glutathione conjugates in human ovarian-carcinoma cell lines. *Int J Cancer* 1993;55:848-856.
38. Slater LM, Sweet P, Stupecky M, Gupta S. Cyclosporin A reverses vincristine and daunorubicin resistance in acute lymphatic leukemia in vitro. *J Clin Invest* 1986;77:1405-1408.
39. Chambers SK, Davis CA, Schwartz PE, Kohorn EI, Chambers JT. Modulation of platinum sensitivity and resistance by cyclosporin

A in refractory ovarian and fallopian tube cancer patients: a phase II study. *Clin Cancer Res* 1996;2:1693-1697.
40. Manetta A, Boyle J, Berman ML, DiSaia PJ, Lentz S, Liao SY, Mutch D, Slater L. Cyclosporin enhancement of cisplatin chemotherapy in patients with refractory gynecologic cancer. *Cancer* 1994;73:196-199.
41. Manetta A, Blessing JA, Hurteau JA. Evaluation of cisplatin and cyclosporin A in recurrent platinum-resistant ovarian cancer: a phase II study of the gynecologic oncology group. *Gynecol Oncol* 1998;68:45-46.
42. Allen TM. Liposomes: opportunities in drug delivery. *Drugs* 1997;54:8-14.
43. Burger KNJ, Staffhorst RWHM, de Vijlder HC, Velinova MJ, Bomans PH, Frederick PM, de Kruijff B. Nanocapsules: lipid-coated aggregates of cisplatin with high cytotoxicity. *Nature Medicine* 2002;8:81-84.
44. Newman MS, Colbern GT, Working PK, Engbers C, Amantea MA. Comparative pharmacokinetics, tissue distribution, and therapeutic effectiveness of cisplatin encapsulated in long-circulating, pegylated liposomes (SPI-077) in tumor-bearing mice. *Cancer Chemother Pharmacol* 1999;43:1-7.
45. Muggia F, Hamilton A. Phase III data on Caelyx® in ovarian cancer. *Eur J Cancer* 2001;37:S15-S18.
46. Rose PG, Maxson JH, Fusco N, Mossbruger K, Rodriguez M. Liposomal doxorubicin in ovarian, peritoneal, and tubal carcinoma: a retrospective comparative study of single-agent dosages. *Gynecol Oncol* 2001;82:323-328.
47. Trimble EL, Arbuck SG, McGuire WP. Options for primary chemotherapy of epithelial ovarian cancer: taxanes. *Gynecol Oncol* 1994;55:S114-S121.
48. Stiff PJ, McKenzie RS, Alberts DS, Sosman JA, Dolan JR, Rad N, McCloskey T. Phase I clinical and pharmacokinetic study of high-dose mitoxantrone combined with carboplatin, cyclophosphamide, and autologous bone marrow rescue: high response rate for refractory ovarian carcinoma. *J Clin Oncol* 1994;12:176-183.
49. Stiff P, Bayer R, Camarda M, Tan S, Dolan J, Potkul R, Loutfi S, Kinch L, Sosman J, Peace D, Rad N, McKenzie RS. A phase II trial of high-dose mitoxantrone, carboplatin, and cyclophosphamide with autologous bone marrow rescue for recurrent epithelial ovarian carcinoma: analysis of risk factors for clinical outcome *Gynecol Oncol* 1995;57:278-285.
50. Raymond E, Faivre S, Chaney S, Woynarowski J, Cvitkovic E. Cellular and molecular pharmacology of oxaliplatin. *Mol Cancer Ther* 2002;1:227-235.
51. Ohno S, Siddik ZH, Baba H, Stephens LC, Strebel FR, Wondergem J, Khokhar AR, Bull JMC. Effect of carboplatin combined with whole body hyperthermia on normal tissue and tumor in rats. *Cancer Res* 1991;51:2994-3000
52. Wallner KE, DeGregorio MW, Li GC. Hyperthermic potentiation of cis-diamminedichloroplatinum(II) cytotoxicity in Chinese hamster ovary cells resistant to the drug. *Cancer Res* 1986;46:6242-6245.
53. Westermann AM, Grosen EA, Katschinski DM, Jager D, Rietbroek R, Schink JC, Tiggelaar CL, Jager E, Zum Vorde sive Vording P, Neuman A, Knuth A, Van Dijk JDP, Wiedemann GJ, Robins HI. A pilot study of whole body hyperthermia and carboplatin in platinum-resistant ovarian cancer. *Eur J Cancer* 2001;37:1111-1117.
54. Yamada K, Hanaoka F, Yamada M. Effects of aphidicolin and/or 2',3'-dideoxythymidine on DNA repair induced in HeLa cells by four types of DNA-damaging agents. *J Biol Chem* 1985;260:10412-10417.
55. 55.O'Dwyer PJ, Moyer JD, Suffness M, Harrison SD, Cysyk R, Hamilton TC. Antitumor activity and biochemical effects of aphidicolin glycinate (NSC 303812) alone and in combination with cisplatin *in vivo*. *Cancer Res* 1994;54:724-729.
56. Moreland NJ, Illand M, Kim YT, Paul J, Brown R. Modulation of drug resistance mediated by loss of mismatch repair by the DNA polymerase inhibitor aphidicolin. *Cancer Res* 1999;59:2102-2106.
57. Alberts DS, Liu PY, Hannigan EV, O'Tooke R, Williams SD, Young JA, Franklin EW, Clarke-Pearson DL, Malviya VK, DuBeshter B, Adelson MD, Hoskins WJ. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *New Engl J Med* 1996;335:1950-1955.
58. Dedrick RL, Myers CE, Bungay PM, DeVita VT Jr. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. *Cancer Treat Rep* 1978;62:1-11.
59. Kirmani S, Lucas WE, Kim S, Goel R, McVey L, Morris J, Howell SB. A phase II trial of intraperitoneal cisplatin and etoposide as salvage treatment for minimal residual ovarian carcinoma. *J Clin Oncol* 1991;9:649-657.
60. du Bois A. Treatment of advanced ovarian cancer. *Eur J Cancer* 2001;37:S1-S7.
61. Clarke-Pearson DL, Van Le L, Iveson T, Whitney CW, Hanjani P, Kristensen G, Malfetano JH, Beckman RA, Ross GA, Lane SR, DeWitte MH, Fields SZ. Oral topotecan as single-agent second-line chemotherapy in patients with advanced ovarian cancer. *J Clin Oncol* 2001;19:3967-3975.
62. Garcia-Carbonero R, Supko JG. Current perspectives on the clinical experience, pharmacology, and continued development of the camptothecins. *Clin Cancer Res* 2002;8:641-661.
63. Thigpen T. The role of gemcitabine-based doublets in the management of ovarian carcinoma. *Semin Oncol* 2002;29(1 suppl 1):11-16.