RESEARCH ARTICLE

Preclinical Activity of Lobaplatin as a Single Agent and in Combination with Taxanes for Ovarian Carcinoma Cells

Xu Sun[1], Li-Guang Lou[3]*, Dong-Hu Sui[1]*, Xiao-Hua Wu[2]

Abstract

Lobaplatin, one of the third - generation platinum compounds, has shown encouraging anticancer activity in a variety of tumor types. However, the efficacy of lobaplatin in ovarian cancer has not been systemically evaluated. In this study, lobaplatin as a single agent and in combination with taxanes was investigated in - vitro and in an *in vitro* model of ovarian carcinoma. Using the sulforhodamine B (SRB) assay, the cytotoxic effects of lobaplatin alone and in combination with taxanes were compared with cisplatin and carboplatin in seven ovarian cancer cell lines. In addition, in - vitro antitumor activities were evaluated with cisplatin - sensitive and cisplatin - resistant human ovarian cancer xenografts in nude mice. The cytotoxicity of lobaplatin was similar to or higher than that of cisplatin and carboplatin, with IC_{50} values from 0.9 to 13.8 μmol/L in a variety of ovarian cancer cells. The combination of lobaplatin with docetaxel yielded enhanced cytotoxic activity *in vitro*. In addition, in platinum - sensitive ovarian cancer xenografts, lobaplatin alone showed similar antitumor activity to cisplatin and carboplatin. Furthermore, lobaplatin alone or in combination with docetaxel exhibited significant activity in platinum - resistant ovarian cancer xenografts. These results indicate that the use of lobaplatin alone or in combination with docetaxel might be a rational and novel therapeutic strategy for ovarian cancer. Further clinical development of lobaplatin is clearly warranted.

Keywords: Lobapaltin - preclinical activity - ovarian carcinoma

Asian Pac J Cancer Prev, **15 (22)**, 9939 - 9943

Introduction

Ovarian cancer is one of the most common gynecologic malignancies (Suh et al., 2012). Because of rare specific symptoms and lack of feasible screening methods, more than two-thirds of patients with ovarian cancer are diagnosed at advanced-stage disease, which leads to poor prognosis. Taxanes and platinum-based chemotherapy after surgery has been established as the first line treatment by previous randomized controlled trials (Ozols et al., 2003; Suh et al., 2012). However, cisplatin has nephrotoxicity, gastointestinal toxicity and neurotoxicity. Myelotoxicity, especially thrombocytopenia has been found to be the dose limiting toxicity of carboplatin. Especially in ovarian cancer, carboplatin appears to have equivalent activity to cisplatin. Besides, cisplatin and carboplatin are cross-resistant (Alberts et al., 1989; Kim et al., 2011). Hence, new effective platinum-based chemotherapeutic agent with less toxicity and non-cross-resistance is needed for the treatment of ovarian cancer.

Lobaplatin (1, 2-diamminomethylcyclobutane-platinum (II)-lactate), one of the third-generation platinum compounds, has shown encouraging anticancer activity in a variety of tumor types such as human esophageal cancer, breast cancer and small cell lung cancer, etc. The preclinical data suggest that the anti-tumour activity of lobaplatin is different from that of cisplatin and carboplatin and might be not cross-resistant (Harstrick et al., 1994; Voegeli et al., 1990; McKeage et al., 2001). Clinically, lobaplatin is tolerable at recommended dosages. Treatment is not associated with any of the typical side effects that are often seen with cisplatin (Gietema et al., 1993). Currently, lobaplatin has been approved in China for the treatment of chronic myelogenous leukemia, metastatic breast cancer and small cell lung cancer. However, the efficacy of lobaplatin in ovarian cancer has not been systemic evaluated yet.

In the current study, lobaplatin as a single agent and in combination with taxane-was investigated *in vitro* and *in vitro* models of ovarian cancer. The results appeared that lobaplatin both alone and in combination with taxane-agents showed comparable efficacy, especially to the SK-OV-3 tumors, which was resistant to cisplatin and carboplatin. These data support the potential clinical use of lobaplatin for the treatment of ovarian cancer.

*[1]The Clinical Department, Guizhou Yibai Pharmaceutical Co.Ltd, Guiyang, [2]The Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center, [3]Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China *For correspondence: lglou@mail.shcnc.ac.cn; suidonghu@sohu.com*

Materials and Methods

Materials

Lobaplatin was provided by Hainan Changan International Pharmaceutical Co. Ltd (Haikou, China). Carboplatin, cisplatin were purchased from Kunming Guiyan Pharmaceutical Co. Ltd (Kunming, China). Paclitaxel and docetaxel were purchased from Jiangsu Yew Pharmaceutical Co. Ltd (Wuxi, China). Paclitaxel and docetaxel were dissolved in dimethylsulfoxide as 10 mmol/L stock solutions (*in vitro*) or in 0.9% NaCl (*in vitro*). The stock solutions were kept frozen in aliquots at -20°C and thawed immediately before each experiment. Carboplatin and lobaplatin were dissolved in pure water as 10mmol/L solutions (*in vitro*) or in 5% glucose (*in vivo*). Cisplatin was dissolved in pure water as 3 mmol/L solutions *(in vitro*) or in 0.9% NaCl (*in vivo*).

Cell culture and treatment

The human ovarian carcinoma cell lines SK-OV-3 and ES-2 were purchased from the American Type Culture Collection (Manassas, Virginia, USA). The cell lines OVCAR-8, SW626, 3AO, OVCAR-3 and OVCAR-3 were obtained from Shanghai Fu Xiang Biotechnology Co. Ltd (Shanghai, China). All these cell lines were maintained in RPMI-1640 or L-15 (Gibco BRL, Carlsbad, CA, USA) supplemented with 10% fetal bovine serumand 100 unites/ml penicillin and 0.1 mg/ml streptomycin at 37°C in a humidified atmosphere containing 5% CO_2.

Measurement of cytotoxicity

To assess the cytotoxic effect of those drugs, a sulforhodamine-B assay was used as described by Skeehan et al (Engel et al., 2012; Skehan et al., 1990; Xie et al., 2012).In Brief, cells were seeded at appropriate densities into 96-well microtiter plates and allowed to attach for 24h. Then the drugs dissolved in growth medium were added at appropriate concentrations for 72h. After 72h drug exposure, the medium was carefully removed and the cells were fixed with 100μl 10% trichloroacetic acid for at least 1h. After being washed five times with tap water, the plates were stained with 0.4% sulforhodamine B in 1% acetic acid for 30 min and again washed five times with 1% acetic acid. The absorbance was read in an automated plate reader at wavelengths of 510 nm. The rate of inhibition of cell proliferation was expressed as the IC_{50}, which is defined as the concentration required for 50% inhibition of cell growth as compared with control cells. The IC_{50} value was determined from the data with a four-parameter logistic equation using GraphPad Prism software (SanDiego, California, USA). Each experiment was carried out in triplicate and was repeated at least three times.

Median-effect analysis for combinations of drugs

The nature of the interaction between platinum-based compounds and taxane-was evaluated by median-effect plot analyses and the combination index (CI) method (Chou et al., 1984; Xie et al., 2012). The agents were combined at the fixed ratios on the basis of the IC_{50} values from singleagent cytotoxicity profiles. Using the mean percentages of cell survival from the SRB assay as a function of drug concentration, the CalcuSyn program (Biosoft, Cambridge, UK) provided a measure of whether the combined agents interacted in an additive, synergistic, or antagonistic manner. Specifically, on the basis of the median-effect principle, CalcuSyn produced a CI value that defined the interaction between two agents as being synergistic (CI<0.95), additive (CI=0.95-1.05), or antagonistic (CI>1.05).

***In-vivo** antitumor activity*

The mice aged 5-6 weeks were purchased from the Shanghai Slaccas Laboratory Animal Co. Ltd (Shanghai, China). Human ovarian carcinoma xenografts of SW626, A2780 and SK-OV-3 cells were established by inoculating the cells intraperitonealy into nude mice (Paine-Murrieta et al., 1997; Xie et al., 2012). Several days later, the mice were assigned randomly to control and treatment groups and treated with vehicle or drugs, respectively. During the experiment, Each group was inspected the mortality and weighed twice weekly. At the end of the experiment, we calculated the rate of survival (RS), the median survival time (MST) and the ratio of life lengthening (RLL) of each group and drew the Kaplan-Meier survival curves to assess the significance.

Results

Lobaplatin inhibits the proliferation of human ovarian carcinoma cells in vitro

The results obtained for the ovarian carcinoma cell lines are listed in Table 1. Lobaplatin showed obvious cytotoxic effects against those cells. The IC_{50} for lobaplatin was between 0.9 and 13.8 μmol/L, which was comparable with that of cisplatin except the line SK-OV-3. Carboplatin was less active than either cisplatin or lobaplatin in all cell lines (Table 1).

Lobaplatin combined with docetaxel shows enhanced in-vitro cytotoxicity in the ovarian carcinoma cell lines

Taxane-and platinum-based chemotherapy has been established as the first line treatment for ovarian cancer by previous studies (Ozols et al., 2003; Suh et al., 2012). In light of this, Cotreatment of platinum-based

Table 1. IC_{50} Values for Cisplatin, Lobaplatin and Carboplatin

Cell line	IC_{50} (μM)		
	Cisplatin	Lobaplatin	Carboplatin
SK - OV - 3	3.1	10.2	104.8
ES - 2	0.9	1.5	14.6
OVCAR - 8	8.1	4.6	96.0
3AO	4.1	3.4	63.4
A2780	7.5	5.8	145.7
SW626	7.0	13.8	97.0
OVCAR - 3	4.1	7.5	32.6

Cells seeded in 96 - well plates were treated with various concentrations of drugs for 72 h. Cell viability was determined by the sulforhodamine B assay. IC_{50} values are shown as the mean of three independent experiments

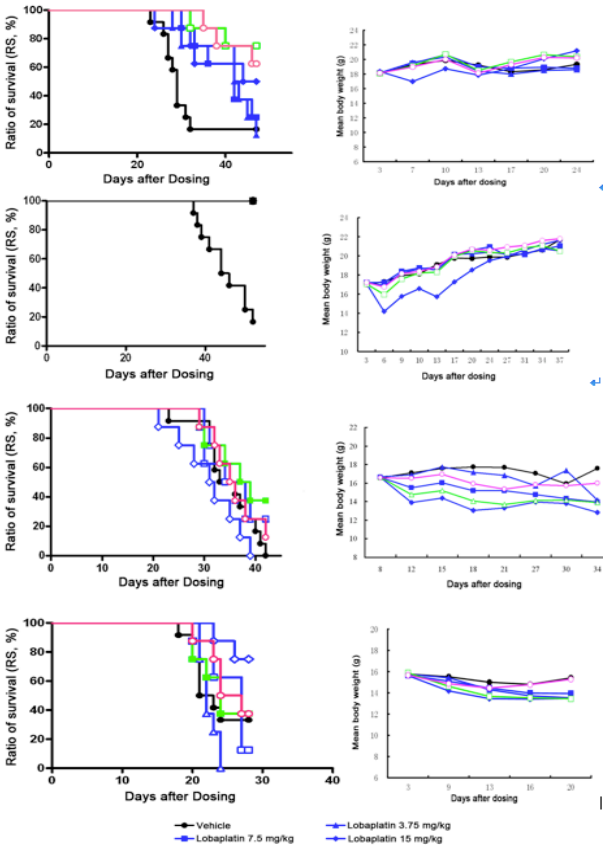

Figure 1. *In vivo* Antitumor Activity of Lobaplatin Alone in Ovarian Carcinoma Xenografts. Human SW626, A2780, SK-OV-3 were implanted intraperitonealy into nude mice. The animals were divided randomly into groups. Control groups received an intraperitoneal injection of normal saline, and treatment groups received an intraperitoneal injection of lobaplatin, cisplatin, or carboplatin. The SW626 xenografts (upper panels) and early period A2780 xenografts (second panels) were injected at the third day (D3) and the tenth day (D10); The advanced period A2780 xenografts (third panels) was injected at the eighth day (D8) and the fifth day (D15); The A2780 xenografts (lower panels) was injected at the sixth day (D6). n=12 in the control and n=8 in the treatment groups

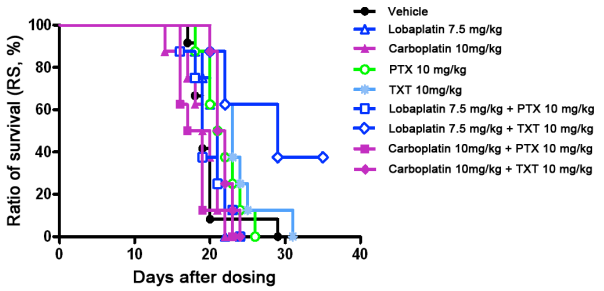

Figure 2. The Antitumor Efficacy of Lobaplatin Combined with Taxanes in SK-OV-3 Xenografts. Mice with established SK-OV-3 xenografts received an intraperitoneal injection of lobaplatin or carboplatin alone in combination with paclitaxel or docetaxel on day 6 and day 13. n=12 in the control and n =8 in the treatment groups

Table 2. Combination Index (CI) for Lobaplatin Combined with Taxanes in Ovarian Cancer Cells

Cell line	CI					
	Paclitaxel +			Docetaxel +		
	Cisplatin	Lobaplatin	Carboplatin	Cisplatin	Lobaplatin	Carboplatin
OVCAR - 8	2.04	1.61	0.68	0.98	1.02	1.23
SK - OV - 3	1.43	1.58	1.97	1.28	0.97	1.26
A2780	1.11	1.37	1.72	1.19	1.05	0.98
SW626	1.38	1.39	1.72	1.38	1.28	1.43

These cells were treated with fixed ratios of platinum - based compounds and antitubulin drugs for 72 h. Cell viability was determined by the sulforhodamine B assay. The effects of the combinations were evaluated by median–effect analysis. CI values <0.95, 0.95–1.05, or >1.05 indicate a synergistic, additive, or antagonistic interaction, respectively

and taxanes was evaluated in OVCAR-8, SK-OV-3, A2780 and SW626 cells. Cells were treated with either lobaplatin, cisplatin, carboplatin or taxane-drugs alone and with a combination of both compounds at different concentrations for 72 h. The results were evaluated by median-effect analysis. Adding docetaxel to lobaplatin clearly increased its cytotoxic effect in OVCAR-8, SK-OV-3 and A2780 cells over the whole dose range (Table 2). As can be extrapolated, these cell lines were highly sensitive to the regimen of lobaplatin and docetaxel. Whereas, only OVCAR-8 and A2780 cells appeared to be sensitive to cisplatin and carboplatin combined with docetaxel, respectively (Table 2). On the other hand, the combination of lobaplatin or cisplatin with paclitaxel generated antagonistic effects in all above cell lines (Table 2). These data indicated the potential clinical use of the regimen of lobaplatin and docetaxel for the treatment of ovarian cancer.

Lobaplatin alone shows potent antitumor activity in vivo against ovarian cancer xenografts

Given its encouraging activity *in vitro*, we investigated the antitumor efficacy of lobaplatin *in vivo*. Specifically, we examined the antitumor activity of lobaplatin against four human ovarian carcinoma xenografts in nude mice, namely, SW626, A2780 (early period, D3), A2780 (advanced period, D8) and SK-OV-3. Before efficacy study, the maximal tolerated doses of lobaplatin, cisplatin, and carboplatin in normal nude mice were first determined. The efficacy of different drugs was compared on the basis of their maximal tolerated dose (i.e. equitoxic dose). Lobaplatin showed similar antitumor activity to cisplatin and carboplatin in platinum-sensitive xenografts obtained from SW626 and A2780 cell lines (Figure 1). However, in the cisplatin-resistant xenografts originating from line SK-OV-3, lobaplatin exhibited antitumor activity stronger than that of cisplatin and carboplatin, thus confirming *in vitro* the lack of cross-resistance seen in the previous experiments (Table 1). On the basis of loss of body weight as a toxic endpoint, cisplatin was the most toxic agent and was more toxic than lobaplatin or carboplatin (Figure 1). The data indicated that lobaplatin alone had potent antitumor activity against ovarian carcinoma *in vivo* and was less toxic than cisplatin.

*Lobaplatin combined with docetaxel shows enhanced **in-vivo** antitumor activity in the cisplatin-resistant ovarian carcinoma xenografts*

The efficacy of lobaplatin in combination with paclitaxel and docetaxel was evaluated in mice injected

i.*p*. with SK-OV-3 cell, which is the cisplatin-resistant ovarian carcinoma cell. Lobaplatin treatments plus docetaxel showed noticeable effects on RS (D52, 62.5%) and MST (29 days) compared with docetaxel treatment alone (D52, 12.5%; 23 days), with 5 of 8 mice from the combined treatment group showing long-term survival at the end of the experiment (D42). The efficacy of lobaplatin/docetaxel was significantly superior to that of carboplatin/docetaxel ($P<0.01$), when compared at equitoxic doses (Figure 2). Consistent with our in-vivo results, the combination of lobaplatin with paclitaxel didn't generate the synergy effect in ovarian carcinoma SK-OV-3 xenografts. In general, the regimen of lobaplatin combined with docetaxel was tolerated without additional toxicity.

Discussion

The platinum-based compounds cisplatin and carboplatin belong to the most frequently used anticancer drugs in clinical practice. Cisplatin has demonstrated high activity in several tumor types, including ovarian carcinoma. Its use, however, is limited by sometimes severe organ toxicity, especially neuro-and nephrotoxicity. Carboplatin shows a favorable spectrum of toxicity, with reversible myelosuppression being the dose-limiting toxicity (Deng et al., 2013; Huang et al., 2013; Peng et al., 2014; Wang et al., 2014; Wu et al., 2014; Zhao et al., 2014). Especially in ovarian cancer, carboplatin appears to have equivalent activity to cisplatin. Besides, cisplatin and carboplatin are cross-resistant. Lobaplatin, as a third-generation platinum complex with reduced nephrotoxicity and incomplete cross-resistance with cisplatin, has potential clinical advantages for certain patients (Oguri et al., 1988; Harstrick et al., 1989; Gietema et al., 1993; Gietema et al., 1995). In the present study, we assessed the in-vitro and in-vitro activities of lobaplatin alone or in combination with taxanes against human ovarian cancer. We demonstrated that lobaplatin alone had significant antitumor activity against human ovarian cancer, and the activity was enhanced when it was combined with taxane-agents, especially with docetaxel. These findings suggest that lobaplatin alone or in combination with docetaxel is a good alternative option for the treatment of ovarian cancer in the clinic.

We chose seven ovarian cancer cell lines to systematically assess the anti-tumour activity of different platinum drugs at doses in micromolar range. In these cell lines, The IC_{50} values determined for lobaplatin in all lines ranged from 0.9 to 13.8 μmol/l. Lobaplatin exhibited cytotoxicity that was comparable in general to that of cisplatin, but significantly stronger than that of carboplatin. In certain cell lines, such as 3AO, OVCAR-8 and A2780, lobaplatin displayed better cytotoxic activity compared with cisplatin. Among these cell lines, SK-OV-3 is relatively sensitive to cisplatin and is relatively insensitive to lobaplatin. Hence, we chose the cell line for the drug combination study and *in vivo* study to further confirm the efficacy of lobaplatin.

platinum-based drugs combined with taxanes is the standard therapy for ovarian cancer (Ozols et al., 2003; Suh et al., 2012) . In light of this, we systemic evaluated the efficacy of lobaplatin in combination with taxanes against ovarian cancer *in vitro* and *in vivo*. In the present study, we found that the combination of lobaplatin with docetaxel produced additive cytotoxicity in most cell lines *in vitro*. The combination of cisplatin or carboplatin with docetaxel generated enhanced cytotoxicity only in OVCAR-8 and A2780 cells, respectively. The enhanced antitumor activity of lobaplatin in combination with docetaxel in the ovarian carcinoma xenografts. The efficacy of lobaplatin in combination with docetaxel was significantly stronger than that of docetaxel or carboplatin/docetaxel, and the combination was well tolerated. However, Compared with lobaplatin/docetaxel, the combination of lobaplatin with paclitaxel was less effective. The similar results could be found in the combination of cisplatin with paclitaxel. These data suggest that lobaplatin combined with docetaxel has superior antitumor activity to cisplatin and carboplatin, and might be a good alternative regimen for chemotherapy of ovarian cancer in clinical.

It was noteworthy that lobaplatin was confirmed to lack complete cross-resistance to cisplatin *in vitro* in previous study (Harstrick et al., 1993). The lack of cross-resistance was further confirmed using platinum-based alone or in combination with taxanes *in vitro* in the present study. A comparison of the RS, MST and RLL values for SK-OV-3 xenografts model, which is cisplatin-resistant, yielded the following rank order (from highest to lowest potency): lobaplatin (7.5 and 15 mg/kg) > carboplatin > cisplatin > lobaplatin (3.75 mg/kg). Besides, the combination of lobaplatin with docetaxel showed better RS and longer MST than that of carboplatin/docetaxel. whereas the exact mechanisms of resistance to cisplatin have not been fully explored. The results of the present study demonstrate that lobaplatin had significant antitumor activity in cisplatin-resistant human ovarian cancer xenograft model in nude mice. It is clinically important that lobaplatin might be a good option for some patients who are resistant to cisplatin. The mechanism of the superior efficacy of lobaplatin compared with cisplatin is currently not known. However, it is suggested that the 1, 2-diamminomethylcyclobutane carrier ligand of lobaplatin, which is significantly different from the cisdiammine carrier of cisplatin and carboplatin, may contribute to the different efficacy, drug resistance, and toxicological profile (Jakupec et al., 2003).

In conclusion, our study could show that the platinum derivative lobaplatin has good antitumour activity against human ovarian cancer both *in vitro* and *in vitro*. In particular, it was shown for the first time that cotreatment with docetaxel substantially increases the cytotoxic effect of lobaplatin, providing a alternative regimen for chemotherapy of ovarian cancer. Moreover, lobaplatin appears to be a lack of complete cross-resistance to cisplatin, and a favorable spectrum of toxicity. Its further clinical development is clearly warranted.

Acknowledgements

We would like to thank Hainan Changan International Pharmaceutical Corporation Limited for partial sponsorship of the study drug. Our study was supported

by grants from Science and Technology Department of Guizhou Province of China (No.2011-5068). There are no conflicts of interest.

References

Alberts DS, Mason L (1989). Carboplatin in the treatment of ovarian cancer. *Seminars Oncol*, **16**, 19-26.

Chou TC, Talalay P (1984). Quantitative analysis of dose-effect relationships, the combined effects of multiple drugs or enzyme inhibitors. *Adv Enzyme Regul*, **22**, 27-55.

Deng QQ, Huang XE, Ye LH, et al (2013). Phase II trial of Loubo® (Lobaplatin) and pemetrexed for patients with metastatic breast cancer not responding to anthracycline or taxanes. *Asian Pac J Cancer Prev*, **14**, 413-7.

Engel JB, Martens T, Hahne JC, et al (2012). Effects of lobaplatin as a single agent and in combination with TRAIL on the growth of triple-negative p53-mutated breast cancers *in vitro*. *Anti-Cancer Drugs*, **23**, 426-36.

Gietema JA, Guchelaar HJ, de Vries EG, et al (1993). A phase I study of lobaplatin (D-19466) administered by 72h continuous infusion. *Anticancer Drugs*, **4**, 51-5.

Gietema JA, De Vries EG, Sleijfer DT, et al (1993). A phase I study of 1, 2-diamminomethyl-cyclobutane-platinum (II)-lactate (D-19466; lobaplatin) admini-stered daily for 5 days. *Br J Cancer*, **67**, 396-401.

Gietema JA, Veldhuis GJ, Guchelaar HJ, et al (1995). Phase II and pharmacokinetic study of lobaplatin in patients with relapsed ovarian cancer. *Br J Cancer*, 71, 1302-7.

Harstrick A, Bokemeyer C, Scharnofkse M, et al (1993). Preclinical activity of a new platinum analogue, lobaplatin, in cisplatinsensitive and-resistant human testicular, ovarian, and gastric carcinoma cell lines. *Cancer Chemother Pharmacol*, **33**, 43-7.

Harstrick A, Casper J, Guba R, et al (1989). Comparison of the antitumor activity of cisplatin, carboplatin, and iproplatin against established human testicular cancer cell lines *in vitro* and *in vitro*. *Cancer*, **63**, 1079-83.

Huang XE, Wei GL, Huo JG, et al (2013). Intrapleural or intraperitoneal lobaplatin for treatment of patients with malignant pleural effusion or ascites. *Asian Pac J Cancer Prev,* **14**, 2611-4.

Jakupec MA, Galanski M, Keppler BK (2003). Tumour-inhibiting platinum complexes state of the art and future perspectives. *Rev Physiol Biochem Pharmacol*, **146**, 1-54.

Kim YH, Kim SC (2011). Recent advances in the biomarkers for epithelial ovarian cancer. *J Gynecol Oncol*, **22**, 219-21.

McKeage MJ (2001). Lobaplatin, a new antitumour platinum drug. *Expert Opin Investig Drugs*, **10**, 119-28.

Oguri S, Sakakibara T, Mase H, et al (1988). Clinical pharmacokinetics of carboplatin. *J Clin Pharmacol*, **28**, 208-15.

Ozols RF, Bundy BN, Greer BE, et al (2003). Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer, a Gynecologic Oncology Group study. *J Clin Oncol*, **21**, 3194-200.

Paine-Murrieta GD, Taylor CW, Curtis RA, et al (1997). Human tumor models in the severe combined immune deficient (scid) mouse. *Cancer Chemother Pharmacol*, **40**, 209-14.

Peng S, Yang QX, Zhang T, et al (2014). Lobaplatin-TACE combined with radioactive 125I seed implantation for treatment of primary hepatocellular carcinoma. *Asian Pac J Cancer Prev,* **15**, 5155-60.

Skehan P, Storeng R, Scudiero D, et al (1990). New colorimetric cytotoxicity assay for anticancer-drug screening. *J Natl Cancer Inst*, **82**, 1107-12.

Suh DH, Kim K, Kim JW (2012). Major clinical research advances in gynecologic cancer in 2011. *J Gynecol Oncol*, **23**, 53-64.

Wang N, Lv YZ, Xu AH, et al (2014). Application of lobaplatin in trans-catheter arterial chemoembolization for primary hepatic carcinoma. *Asian Pac J Cancer Prev,* **15**, 647-50.

Wu XY, Huang XE, Cao J, et al (2014). A predictive model for evaluating responsiveness to pemetrexed treatment in patients with advanced colorectal cancer. *Asian Pac J Cancer Prev,* **15**, 5941-4.

Xie C-Y, Xu Y-Pg, Jin W, Lou L-G (2012). Antitumor activity of lobaplatin alone or in combination with antitubulin agents in non-small-cell lung cancer. *Anti-Cancer Drugs*, **23**, 698-705

Voegeli R, SchumacherW, Engel J, et al (1990). D-19466, a new cyclobutane-platinum complex with antitumor activity. *J Cancer Res Clin Oncol*, **116**, 439-42.

Zhao C, Wang XJ, Wang S, et al (2014). Lobaplatin combined floxuridine/pirarubicin-based transcatheter hepatic arterial chemoembolization for unresectable primary hepatocellular carcinoma. *Asian Pac J Cancer Prev,* **15**, 2057-60.